COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE

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Dedicated

to

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LIST OF ABBREVIATIONS

ACR- ALBUMIN-TO-CREATININE RATIO

AER- ALBUMIN EXCRETION RATE

AKI – ACUTE KIDNEY INJURY

CAD – CORONARY ARTERY DISEASE

CKD – CHRONIC KIDNEY DISEASE

CKD-DD – CHRONIC KIDNEY DISEASE DIALYSIS DEPENDENT

CKD-ND – CHRONIC KIDNEY DISEASE NON-DIALYSIS DEPENDENT

COPD – CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DM – DIABETES MELITUS

EGFR- ESTIMATED GLOMERULAR FILTRATION RATE

GBM- GLOMERULAR BASEMENT MEMBRANE

GFR – GLOMERULAR FILTRATION RATE

HTN – HYPERTENSION

KDIGO - KIDNEY DISEASE IMPROVING GLOBAL OUTCOME

PER - PROTEIN EXCRETION RATE

RBC- RED BLOOD CELL

WBC- WHITE BLOOD CELL

ABSTRACT

INTRODUCTION: An impaired kidney function and a progressive decrease in the GFR are linked to a range of pathophysiological processes that collectively constitute Chronic Kidney Disease. The KDIGO classification is used to classify CKD, when renal failure advances from stage III (GFR - 45–59 ml/min or 1.73 m2) to stage V (GFR < 15 ml/min or 1.73 m2), phosphate binders are required, and dialysis may or may not be necessary. Ferric citrate was first prescribed for CKD-DD patients as a phosphate binder; however, a new study has indicated that CKD-ND patients may potentially benefit from using this medication. CKD-ND patients with hyperphosphatemia, on the other hand, can benefit from the use of sevelamer carbonate, an enhanced buffered version of sevelamer hydrochloride.

OBJECTIVES: To study the efficacy and compare ferric citrate and sevelamer carbonate in patients of non-dialysis dependent chronic kidney disease.

METHODS: A prospective observational study was conducted at Dayanand Medical College and Hospital, Ludhiana, Punjab, India. Including patients with non-dialysis dependent chronic kidney disease stage - III to V according to KDIGO classification with hyperphosphatemia (>4.5) for 12 Months including 3 months of follow-up.

RESULTS: Out of 100 patients, 26 patients in the FC group and 24 in the SC group were male and female, respectively. In the FC group, the majority of patients belonged to CKD IV (76%) > CKD III (16%) > CKD V (8%). SC group patients were primarily from CKD category IV (78%) > CKD V (12%) > CKD III (10%). The majority of patients in both groups (82% - FC) and (88% - SC) were >40 years of age. When compared to sevelamer carbonate therapy administered over 12 months, ferric citrate has demonstrated a better response in raising serum iron levels, ferritin, transferrin saturation, and hemoglobin while lowering serum parathyroid levels, total iron binding capacity (TIBC), and serum alkaline phosphate in patients with CKD. On the other hand, sevelamer carbonate, when administered over 12 months of therapy, has demonstrated a superior response to ferric citrate in lowering serum calcium levels in individuals with CKD. When administered over 12 months to patients with CKD, ferric citrate is non-inferior to sevelamer carbonate in decreasing serum phosphorus levels.

CONCLUSION: Ferric citrate can be considered over sevelamer carbonate as it has a better response on anemia profile and non-inferior phosphorus reduction when compared to other phosphate binders in patients with CKD-ND - III TO V.

KEYWORDS: chronic kidney disease, ferric citrate, sevelamer carbonate.

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INTRODUCTION

Long-term decrease of kidney function is a common disorder known as chronic kidney disease (CKD). It is mostly diagnosed in the presence of other co-morbidities like - hypertension, diabetes Mellitus, and cardiovascular disease. Only the presence of features of chronic kidney disease is the exception rather than the rule, and CKD is associated with poor socioeconomic status. [1-3]

Chronic kidney disease-mineral and bone disease (CKD-MBD) indicates a complicated clinical illness that includes abnormalities in the metabolism of FGF23, phosphate, calcium, vitamin D, and PTH, these abnormalities result in changes in bone structure (renal osteodystrophy), and cardiovascular calcification, and cardiovascular mortality. [4]

Table 1: The following are the risk factors seen in people progressing to CKD: [5]

1. Diabetes	
2. Hypertension	
3. Acute kidney injury	
4. cardiovascular disease	I. ischemic heart disease II. chronic heart failure III. peripheral vascular disease IV. cerebral vascular disease
5. Renal	I. Structural renal tract disease, II. Renal calculi, III.Prostatic hypertrophy
6. Multisystem diseases with potential kidney involvement	Systemic lupus erythematosus
7. Hereditary kidney disease or end-stage renal illness (GFR category G5) in the family history	
8. Opportunistic detection of hematuria	

Table 2: Diagnostic criteria for CKD: [5]

One of the following needs to be present for > 3 months:	
a) Decreased eGFR (<60 mL/min/1.73 m2)	
b) One or more markers of kidney damage:	I. Albuminuria (urinary albumin-to-creatinine ratio [ACR] ≥30 mg/g [3 mg/mmol] II. Structural abnormalities (from imaging) III. Abnormalities of the urine sediment (granular casts, casts of red or white blood cells, oval fat bodies or fatty casts, hematuria, and renal tubular epithelial cells" IV. Electrolyte and other abnormalities due to tubular disorders V. Histological abnormalities VI. Previous history of kidney transplantation.

Effective identification of the presence of CKD and management for the same is necessary to prevent CKD progression and other associated complications of CKD. It decreases the risks associated with acute kidney injury (AKI) and improves patient safety and medical management of the patient.

- **MANAGING PEOPLE WITH CKD:** Physicians are crucial to the monitoring and treatment of CKD, especially when it comes to lowering the risk of cardiovascular disease and other consequences. The percentage of patients having mild-moderate CKD who develop end-stage disease is very small.

  In the HUNT II trial, population-based research conducted in Norway, out of 3,069 individuals with chronic kidney disease (CKD) monitored

for a median of 8 years, only 38 (1%) developed end-stage disease.[6] Thus, the primary goal of medical management and monitoring for individuals with chronic kidney disease (CKD) is risk stratification, which involves objective measurements and clinical judgment in consultation with the patient.

This risk must be routinely reviewed to identify individuals at risk of other complications, such as cardiovascular disease and acute kidney injury, in addition to the small percentage of individuals who are at risk of the disease progressing.

The two main independent risk factors for the poor cardiovascular outcomes that typically occur in patients with CKD are hyperphosphatemia and increased levels of fibroblast growth factor 23 (fgf23).

As chronic kidney disease advances, the risk of hyperphosphatemia rises because the kidney's capacity to excrete phosphate is reached. In the early stages of the disease, compensatory increases in fibroblast growth factor - 23 (fgf23) and PTH prevent phosphate from being reabsorption by the proximal renal tubules, keeping serum phosphate levels within the normal range.

Elevated serum phosphate levels in patients with CKD are linked to higher mortality, vascular calcification, and the course of the disease.

Ferric citrate and sevelamer carbonate are two intestinal phosphate binders that are being utilized to correct hyperphosphatemia in chronic renal disease.

- **CKD PROGRESSION:** Identifying CKD patients who are most at risk of progression has been the focus of several research. Optimizing the use of currently available biomarkers, both separately and in combination, has been a part of this. Peralta et al [7] showed that combining eGFR defined by creatinine with eGFR generated from ACR and cystatin C enhanced the capacity to identify individuals at higher risk of progression and death early on. Numerous risk stratification models have been created (a recent systematic evaluation found 23 distinct models), most notably from the viewpoint of the population of

individuals with CKD, developed by Tangri et al [8,9] which included People at risk of progression can be identified using widely accepted epidemiological measures, clinical findings, and other relevant markers.

Numerous other noteworthy risk factors have also been investigated, such as fibroblast growth factor 23, genetic markers, and additional inflammatory markers like serum-free light chains and circulating receptors for tumor necrosis factor. More recent cardiovascular risk factors include CXC motif, ligand 12, and ceruloplasmin.[10]

- **KIDNEY DAMAGE:**

The most common method of determining kidney damage is by using markers rather than a direct examination of kidney tissue.
Damage might affect the parenchyma, major blood arteries, or collecting systems.

1. Proteinuria. A higher-than-normal level of urinary protein is referred to as proteinuria.

2. Albuminuria. Abnormal albumin loss in urine content. One form of plasma protein that is present in the urine of healthy individuals and at higher concentrations in renal disease patients is albumin.
3. Urine sediment abnormalities: In many kidney and urinary tract diseases, elements like cells, casts, crystals, and microorganisms can be found in the urine sediment. However, renal tubular cells, red blood cell (RBC) casts, white blood cell (WBC) casts, coarse granular casts, wide casts, and a high concentration of dysmorphic RBCs are pathognomonic of kidney damage.

4. Abnormalities in electrolytes due to tubular disorders: Renal tubular secretion and reabsorption disorders may lead to electrolytes and other solute abnormalities. Although rare, these disorders are indicative of renal disease.

When there are no underlying pathologic problems, the diseases are frequently genetic. Other disorders are acquired, typically accompanied by large tubular pathologic lesions, and are caused by medications or toxins.

5. Metabolic and endocrine complications: Anaemia, acidosis, malnutrition, and problems with bones and minerals are among the consequences that arise when eGFR falls and indicate a lack of endocrine or exocrine function of the kidneys.

- **CHRONIC KIDNEY DISEASE–MINERAL BONE DISORDER (CKD-MBD):**

Disturbances in phosphate, calcium, PTH, vitamin D, and FGF23 levels are characteristics of the multifactorial disease known as chronic kidney disease-mineral bone disorder (CKD-MBD). Changes in bone morphology and systemic effects result from these changes, with higher death rates mostly from cardiovascular problems. Inconsistencies in blood phosphorus, calcium, PTH, and vitamin D are crucial to CKD-MBD, impacting bone health and extra-skeletal calcifications.

Research points to their links to unfavorable outcomes, such as the elevated risk of fractures and cardiovascular death. Phosphate, calcium, vitamin D, and PTH levels are controlled using radiological imaging and blood testing to diagnose and treat metabolic disorders and individual patient features. High death rates could result from these anomalies, primarily from cardiovascular problems.

Many clinical guidelines that prescribe particular laboratory objectives and therapeutic strategies to ameliorate the morbidity and mortality associated with this systemic illness have been developed since the term CKD-MBD was first described.

- Significant features of this syndrome include:
    - Decreased serum Calcium

- Increased serum Phosphorus
- Increased serum PTH
- Decreased Serum Vitamin D
- And the impact of the above on mineralization, extra-skeletal calcifications, and bone turnover.

By using bone biopsy histomorphometry, CKD-MBD can be evaluated. Certain components, like loss of the transmembrane protein (Klotho), increased FGF23 secretion, decreased rates of bone synthesis, and vascular calcification, frequently occur before abnormal biochemical markers manifest, even though the majority of features appear when the GFR drops below 40 mL/min.[11][12]

Strong evidence points to a link between these disorders and several unfavorable clinical outcomes, most notably elevated risk of fracture and cardiovascular death. The functions of FGF23, Klotho, Wnt inhibitors, and activin A are among the important findings about the pathophysiology of CKD-MBD that are highlighted in this activity.

The main goal of CKD-MBD management approaches is to avoid side effects brought on by secondary hyperparathyroidism. So, recognized proxy indicators of disordered mineral bone metabolism, such as blood calcium, phosphate, PTH, and 25-hydroxyvitamin D, serve as a guide for managing secondary hyperparathyroidism.[13][14]

Changes in bone morphology are represented by renal osteodystrophy, a feature of CKD-MBD. Despite being the most reliable method for diagnosis and classification, a biopsy from bone is a procedure that is not often carried out. Monitoring the serial fashion of biochemical markers is advised by KDIGO for continued management of renal osteodystrophy.

Before the identification of fibroblast growth factor 23 (FGF23), the primary cause of secondary hyperparathyroidism was thought to be phosphate retention brought on by a decrease in renal function. [15]

➢ The Triple Threat:

1. Hyperphosphatemia

2. Low 1, 25$(OH)_2$D3

3. Hypocalcaemia

Caused by retained phosphate is well-known for stimulating PTH secretion, which in turn promotes phosphate excretion and the development of secondary hyperparathyroidism in advanced chronic kidney disease. Secondary hyperparathyroidism's pathogenesis is a complicated process involving multiple elements interacting. According to the accepted theory, secondary hyperparathyroidism develops as a trade-off between PTH and the normalization of calcium and phosphate levels. [16,17]

Studies showing a correlation between high phosphate diets and parathyroid hyperplasia provided more evidence for the function of phosphate in the pathophysiology of secondary hyperparathyroidism. [18,19] The discovery of FGF23, for instance, has fundamentally changed our knowledge of the processes that lead to secondary hyperparathyroidism. As renal function deteriorates, plasma FGF23 levels rise, usually ahead of noticeable alterations in phosphate and PTH levels.[20] The function of FGF23 in the Pathophysiology of Secondary Hyperparathyroidism Stem cell-derived fibroblast growth factor 23 (FGF23) is essential for the metabolism of phosphate and vitamin D. It binds to the FGF receptor (FGFR) in traditional target organs like the kidneys and parathyroid glands, but it needs the transmembrane protein (klotho) to do so. [21] In addition to potentially reducing intestinal phosphate absorption by blocking NaPi cotransporter activity, plasma FGF23 increases phosphate excretion in the proximal renal tubule by reducing the expression of luminal sodium-dependent phosphate transporters [22]

Furthermore, by downregulating the activity of 1α-hydroxylase and enhancing the activity of 24-hydroxylase, it decreases the production of 1,25-dihydroxy vitamin D [1,25$(OH)_2$D3].[23] Early in CKD, high FGF23 levels restrict 1,25(OH)2 vitamin D levels by attenuating hyperphosphatemia. This sets the foundation for the development of secondary hyperparathyroidism.[23]

Table 3: Markers of bone turnover [24]

Marker	Origin	Specimen
Bone formation Specific bone alkaline Phosphatase (b-alp)	Bone	Serum
Osteocalcin (OC)	Bone, platelets	Serum
C-terminal pro-peptide of type I procollagen (PICP)	Bone, soft tissue, skin	Serum
N-terminal pro-peptide of type I procollagen (PINP)	Bone, soft tissue, skin	Serum
Bone resorption Hydroxyproline	Bone, cartilage, soft Tissue, skin	Urine
Hydroxylysine glycosides	Bone, soft tissue, skin, serum & complement	Urine, serum
Carboxyterminal crosslinked Telopeptide of type I collagen (CTX-I)	Tissues containing Type I collagen	Urine, serum
Amino-terminal crosslinked Telopeptide of type I collagen (NTX-I)	Tissues containing Type I collagen	Urine, serum
Bone sialoprotein (BSP)	Bone, dentin, Hypertrophic cartilage	Serum
Tartrate-resistant acid Phosphatase (TRACP)	Bone, blood	Plasma, serum

NEED FOR THE STUDY

Anemia, heart failure, central nervous system dysfunction (cognitive), and a reduction in health-related quality of life are all associated with iron deficiency in people with chronic renal disease. On the other hand, secondary hyperparathyroidism, dystrophic calcification, and other anomalies of mineral metabolism can be attributed to hyperphosphatemia. It is **unknown** what the best management approaches are for iron deficiency and phosphate retention in advanced non-dialysis chronic kidney disease (NDD-CKD).

When Ferric Citrate was first used, it was approved as a phosphate binder and was used to regulate serum phosphorus in dialysis-dependent chronic kidney disease (DD-CKD). Ferric citrate is effective in treating hyperphosphatemia in patients with dialysis-dependent chronic kidney disease (DD-CKD). It has been shown to increase serum ferritin and transferrin saturation (TSAT) and decrease serum phosphate concentrations, allowing patients to maintain healthy Hemoglobin levels while taking fewer erythropoiesis-stimulating agents (ESAs) and intravenous irons.

Sevelamer carbonate is an anion-exchange resin that functions similarly to sevelamer hydrochloride, except that carbonate acts as an anion in place of chloride. Bicarbonates are produced when carbonate is substituted for chloride in patients with chronic kidney disease who are not receiving dialysis, are susceptible to acidosis, and are not receiving renal replacement therapy. In patients receiving haemodialysis for chronic kidney disease, sevelamer carbonate and hydrochloride had equivalent safety and effectiveness profiles.

Phosphate binders, which include ferric citrate and sevelamer carbonate, are being investigated in several studies for their potential to effectively treat hyperphosphatemia and other mineral abnormalities in patients with chronic renal disease.

However, the comparative efficacy in a patient of non-dialysis-dependent chronic kidney disease is **UNKNOWN**, when compared to which one is more efficacious and should be used more often for the benefit of the patient in reducing morbidity and premature mortality associated with chronic kidney disease.

THAT IS WHAT THIS STUDY AIMS TO ACHIEVE.

AIMS AND OBJECTIVES

1. To study the efficacy of ferric citrate and sevelamer carbonate in patients with non-dialysis-dependent chronic kidney disease.
2. To compare the efficacy of ferric citrate and sevelamer carbonate in patients of non-dialysis dependent chronic kidney disease.

REVIEW OF LITERATURE

A serious global public health concern, chronic kidney disease is a leading cause of morbidity and early death. Anemia, accelerated vascular disease, and problems with minerals and bones are the underlying causes of these numerous chronic kidney disease consequences.

One of the many features of chronic kidney disease-mineral bone disorder (CKD-MBD) includes disturbances in phosphate, calcium, PTH, vitamin D, and fibroblast growth factor-23 (FGF23) levels. As they affect bone health and extra-skeletal calcifications, blood calcium, phosphorus, PTH, and vitamin D fluctuations are critical to CKD-MBD. Increased death rates, primarily from cardiovascular issues, are the consequence of changes in bone morphology and systemic effects. Their associations with adverse consequences, including high fracture risk and cardiovascular death, have been demonstrated by clinical trials.

An important feature of this disease is the abnormalities in the serum lev
els of calcium, phosphorus, vitamin D, PTH, and calcium. Bone biopsy histomorphometry can be used to evaluate CKD-MBD. These abnormalities also affect mineralization, extra-skeletal calcifications, and the metabolism of bones. There is substantial evidence linking these illnesses to several poor clinical outcomes, most notably an increased risk of cardiovascular mortality and fracture.

Renal osteodystrophy, a characteristic of CKD-MBD, is a representation of changes in bone morphology. A bone biopsy is a rare procedure, yet it is the most reliable tool for diagnosis and categorization. Renal osteodystrophy should be managed according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines, which include tracking the serial trend of biochemical markers.

The development of glomerular filtration rate (GFR) decreases and changes in bone composition and systemic mineral metabolism are symptoms of chronic kidney disease (CKD). CKD-mineral bone disease (MBD) is the term for the condition where bone microstructure and remodelling deteriorate due to disrupted mineral metabolism as GFR loss worsens. A larger systemic condition of mineral and bone metabolism as a result of CKD was defined as CKD-MBD by The Kidney Disease: Improving Global Outcomes (KDIGO). [25] The following traits define CKD-MBD: abnormalities in mineralization, bone turnover, volume linear growth, or strength:

- Abnormalities in phosphorus, calcium, parathyroid hormone (PTH), or vitamin D metabolism
- Abnormalities in soft-tissue calcification, either vascular or extra-osseous.[26]

➢ EPIDEMIOLOGY:

A variety of symptoms can be seen in CKD-MBD, and the prevalence of the condition varies according to its particular features. For instance, arterial morphometry reveals higher medial thickness in dialysis patients, who are more likely to experience vascular calcification.[27] Eighty percent of dialysis patients experience coronary artery calcification, which is more common as GFR decreases and starts early in vascular calcification.[28,29] Studies have reported varying prevalence rates for CKD-MBD; for instance, recent data based on the Kidney Disease Outcomes Quality Initiative (KDOQI) suggest a prevalence of 55%, while the KDIGO guidelines estimate it at 86%.[30]

Adynamic bone disease is now more common in the past several decades, replacing hyperparathyroidism-induced high bone turnover illnesses. [31] This change is thought to be caused by several variables, including excessive use of vitamin D analogues, which inhibit PTH. [32] PTH levels are similarly impacted by phosphate binders that include calcium. Diabetes patients on maintenance dialysis also frequently

have lower PTH levels than non-diabetic patients, which increases the risk of poor bone turnover. [33] Increased use of non-aluminum phosphate binders and improved techniques for cleaning the water used to prepare the dialysate have led to a decrease in osteomalacia, which is another factor leading to the rise in adynamic bone disease. [34,35]

- **PATHOPHYSIOLOGY:**

Based on the various ways that CKD-MBD presents, the pathophysiology of the illness may be broken down into several parts. Skeletal and extra-skeletal aspects of this illness can be distinguished.

1. Abnormalities of the skeleton in renal osteostrophy (CKD-MBD)

Histologically, renal osteodystrophy—the skeletal manifestation of chronic kidney disease—is categorised into states with high or low bone turnover. A mixed-uremic osteodystrophy is a third group that presents with aberrant mineralization features and both low and rapid bone turnover. High-turnover osteitis fibrosa cystica and low-turnover abnormalities in mineralization, as seen in osteomalacia, are characteristics of mixed uremic osteodystrophy. [36] In addition to bone diseases, CKD-MBD is known to include muscular weakness, myopathy, and calcifications.[37]

2. High bone turnover: Higher rates of both bone production and resorption define conditions with high bone turnover. These conditions, which can present as primary, secondary, or tertiary hyperparathyroidism, are significantly influenced by elevated PTH levels in their etiology. When parathyroid gland adenomas secrete PTH on their own, it can result in tertiary hyperparathyroidism and a rapid turnover rate of bone.[38] Osteitis fibrosa cystica is an uncommon consequence of end-stage high-turnover bone disease. It is characterised by accelerated bone turnover as a result of secondary hyperparathyroidism. The characteristic hemosiderin deposits known as "brown tumours" are the result of this accelerated turnover. For further details, view the related resource "Osteitis Fibrosa Cystica," available through Stat Pearls. [39]

3. Low bone turnover: Osteomalacia and adynamic bone disease, which are prevalent in individuals with end-stage renal illness, are the main conditions of low bone turnover. The following are important elements that contribute to pathogenesis:

- Osteomalacia: Intoxication with heavy metals, primarily aluminium, can cause osteoblasts and osteoclasts to malfunction. An overabundance of bone matrix accumulates, and bone mineralization is impaired as a result of dysfunctional osteoblasts. There have also been accusations against other metals, including iron and cadmium. However, in recent decades, this kind of osteomalacia has become less common.
- Adynamic bone disease: The primary cause of adynamic bone disease is reduced PTH levels, which lead to limited bone turnover and inadequate bone mineralization without the excessive osteoid deposition seen with osteomalacia. Skeletal resistance to PTH is a major contributing element to the rising prevalence of this illness over time.[40]

Adynamic bone disease is influenced by several factors, like:

- CKD patients who receive aggressive calcium and vitamin D therapy experience prolonged PTH suppression. [41,42]
- Bone turnover indicators show that supplementing with calcitriol, or activated vitamin D, can decrease bone turnover. Nevertheless, it is unclear how this happens, such as via lowering PTH levels [43]
- Constant ambulatory peritoneal dialysis: This condition causes the dialysate to significantly increase the body's intake of calcium.
- Evidence for diabetes mellitus indicates that suppressed PTH production is linked to increased glucose and decreased insulin levels. [43,44]

Additional variables: The pathophysiology of adynamic bone disease also involves other factors that play secondary roles, such as interleukin-4 and a lack of osteogenic protein-1.[38]

EXTRA-SKELETAL MANIFESTATIONS:

Evidence of the widespread systemic impact of CKD and CKD-MBD, particularly on cardiovascular health, is mounting, even though skeletal symptoms (renal osteodystrophy) have garnered the majority of focus. Other impacted bodily systems include dementia, anemia, constipation, inflammation of the liver, cancer, infection, and malnourishment.

1. **Vascular calcification**: Because of its link to morbidity and mortality, vascular calcification in CKD-MBD has been thoroughly investigated. It is now understood that vascular calcification is an actively controlled process, akin to bone formation, rather than a passive byproduct of degenerative aging. Complex interactions between calciprotein particles (CPPs), the extracellular matrix, and vascular smooth muscle cells are involved in the process. These particles include fetuin-A, calcium, phosphate, and other proteins. They were generated in settings with high levels of these nutrients. CPPs can cause extracellular matrix calcification, apoptosis in smooth muscle cells, and inflammatory reactions. [45,46] In the uremic milieu that characterises chronic kidney disease (CKD), calcification inhibitors like pyrophosphate and fetuin-A decrease while calcification promoters like calcium and phosphate increase. [47] Moreover, increased vascular stiffness and endothelial dysfunction are linked to lower calcitriol levels. [48]

2. **Cardiac abnormalities:** In CKD-MBD, cardiac abnormalities are common and have a major impact on morbidity and death. Cardiovascular events are linked to elevated levels of FGF23 and PTH. Atrial fibrillation and cardiomyocyte hypertrophy are associated with FGF23-mediated activation of distal tubular sodium-chloride cotransporters, which raises the risk of volume overload. [48] Lower concentrations of Klotho, a protein that is depleted in chronic kidney disease, may provide cardioprotective benefits. Heart fibrosis and left ventricular hypertrophy have been shown in animal experiments using Klotho knockout mice. [49] Osteoblast-like

cells in cardiac valves are thought to be responsible for valve illness because they generate peptides linked to bone and aid in the calcification of extracellular matrix.[48]

3. **Neurological events:** Increased levels of FGF23 have been related to neurological events such as dementia, minor cerebral vascular disease, and cognitive loss, according to data taken from the Framingham Heart Study. [50][37] Hyperphosphatemia was connected to brain haemorrhage, whereas hypophosphatemia was linked to brain ischemia events, according to large prospective research including hemodialysis patients. [51] High PTH levels were linked to an increased risk of myocardial infarction and hemorrhagic stroke, according to another extensive longitudinal investigation. Hyperphosphatemia and hypercalcemia were also shown to be associated with a higher risk of brain haemorrhage in this investigation. It is believed that in cases of hypercalcemia and hyperphosphatemia, cathepsin S, enhanced vascular smooth muscle disruption caused by matrix metalloproteinases II and IX, and vascular calcification are to blame. [52]

4. **Gastrointestinal effects:** Constipation, inflammation of the liver, and changes to the intestinal flora are among the gastrointestinal side symptoms linked to CKD-MBD. [53] The native gut flora can be affected by uremic toxins, phosphate binders, hyperphosphatemia, and dietary limitations. Newer iron-containing binders may have less of an impact on the microbiota than older calcium-containing phosphate and anion-exchange binders, albeit the studies are still preliminary. [54-56]

5. **Infections:** Evidence suggests a connection between infection-related mortality and CKD-MBD. Infections are the second-most common cause of death for patients on hemodialysis. PTH and FGF23 excess can impede leukocyte recruitment and compromise the host immunological response. Patients receiving hemodialysis

who have hypercalcemia also had higher all-cause mortality and infection-related mortality rates. Perhaps as a result of impaired leukocyte function or increased levels of FGF23 and CPPS, this impact is more pronounced in younger patients and those with hypoalbuminemia.[57] Studies indicating a decrease in severe sepsis in individuals on calcium channel blockers provide more evidence for this correlation. [58,59]

6. **Malnutrition:** End-stage renal disease patients frequently suffer from malnutrition as a result of uremic toxins, persistent inflammation, protein loss during dialysis, and dietary restrictions. Research has shown that elevated levels of C-reactive protein and inflammatory indicators are correlated with enhanced FGF23 levels. Additionally, increased PTH has been shown in animal models to contribute to cachexia by turning white adipose tissue brown. [53] Furthermore, the Dialysis Outcomes and Practice Patterns Study's findings indicate a separate impact beyond hunger measurements, since higher PTH levels are associated with more weight loss. [60]

7. **Miscellaneous:** Common metabolic problems and related bone diseases cause symptoms in patients with CKD-MBD. Over time, people with hyperparathyroidism may develop noticeable symptoms such as proximal myopathy and bone pain.

   Initially, the condition may not cause any symptoms. The delayed emergence of symptoms means that they are frequently not reported until the right treatment is started, relieving the discomfort. The metaphyseal erosion of long bones in parathyroid illness can cause substantial bone abnormalities in children and teenagers quickly, even though fractures are rare in this condition. The effectiveness of erythropoietin treatment may potentially be compromised by hyperparathyroidism.

Symptoms of aluminium-induced osteomalacia syndrome include proximal myopathy, recurrent fractures, and widespread bone pain. The axial skeleton and proximal muscles are involved, which points to osteomalacia and aluminum poisoning. [61] Dementia and hypochromic anaemia can result from excessive total body aluminum. However, because more people are aware of the dangers of aluminum, this presentation is becoming less frequent. There are other recognized lesser types of aluminum-associated bone disease and a combined form of aluminum and parathyroid illness. These illness types typically cause patients to have fewer symptoms. Children and younger patients tend to acquire aluminum in their bones more quickly than older patients do, and individuals with type 1 diabetes tend to deposit aluminum more readily.

Symptoms of low turnover states are more widespread and result in faulty mineralization and an inability to heal continuing damage. Adynamic bone disease has arisen as a result of growing understanding and the creation of treatments to inhibit hyperparathyroidism. For those suffering from adynamic bone disease, bone pain is the most common symptom. [62] Additionally, these individuals are more likely to fracture, and children may experience developmental retardation. The low structural integrity of bones linked to adynamic bone disease may possibly be the cause of these individuals' higher fracture incidence. The risk of vascular calcification is increased when the parathyroid gland is suppressed by maintaining greater plasma calcium concentrations.

In addition to having an excessively suppressed PTH level, patients with adynamic bone disease cannot frequently buffer calcium on the bone, which causes hypercalcemia. [63] Importantly, vascular calcifications might have symptoms peculiar to a particular place. Blood artery calcifications can produce persistent hypertension, which raises the risk of cardiovascular events and strokes, which are major causes of death for CKD patients. They can also increase

pulse pressure and wall stiffness. [64] Furthermore, calciphylaxis is linked to hyperphosphatemia, hypercalcemia, and increased PTH levels. [65] Renal osteodystrophy symptoms in children with CKD include avascular necrosis, bone discomfort, growth failure, and skeletal abnormalities. [66] There are a few rare instances of patients with renal osteodystrophy-related jugular foramen stenosis resulting in intracranial hypertension.[67] Osteosclerosis, osteomalacia, cortical bone erosion, brown tumors, and lamina dura resorption are signs of renal osteodystrophy resulting from secondary hyperparathyroidism in cranial bones. Rarely documented in the literature, uremic leontiasis ossea is very severe osseous disorders, characterized by significant thickening of the skull and face bones. [68]

➢ ETIOLOGY

The multifactorial illness known as CKD-MBD is typified by abnormalities affecting many physiological systems, including skeletal, non-skeletal, biochemical, and morphological. The following list includes the main etiological factors that lead to the development of CKD-MBD.

- **Impaired Renal Function:** In patients with CKD, impaired kidney function plays a crucial role in the development of CKD-MBD. Calcium and phosphate levels are among the minerals and electrolyte balances that the kidneys preserve. This delicate equilibrium is upset as kidney function declines, which plays a part in the development of CKD-MBD.
- **Dysregulated Calcium, Vitamin D, And Phosphate Homeostasis:** Impaired phosphate excretion and decreased synthesis of active vitamin D (calcitriol or 1,25 dihydroxy vitamin D) cause dysregulated phosphate, vitamin D, and calcium, homeostasis in individuals with chronic kidney disease (CKD), which results in hyperphosphatemia and hypocalcemia. These abnormalities lead to negative consequences such as vascular

calcification linked to chronic kidney disease and myocardial infarction.

- **Abnormal PTH Regulation:** Secondary hyperparathyroidism arises from the dysregulation of PTH due to impaired kidney function in chronic kidney disease (CKD). The calcium balance in the skeletal system is upset by excessive PTH secretion, which is triggered by high phosphate, low calcium, and insufficient vitamin D levels.This results in bone resorption and calcium release. The primary cause of renal osteodystrophy is secondary hyperparathyroidism.
- **Secondary Hyperparathyroidism:** One important symptom of CKD-MBD is secondary hyperparathyroidism, which is frequently identified and tracked by PTH levels. The following consequences of excessive PTH secretion, which are caused by a variety of events that start and continue the disease, include
- Decreased free ionized calcium concentration
- Increased FGF23 concentration
- Decreased expression of calcium-sensing receptors (CaSRs), FGF receptors, and vitamin D receptors in the parathyroid glands[69]
- Decreased calcitriol concentration
- Phosphate retention

Understanding the significance of these variables in the development of secondary hyperparathyroidism can be gained by looking at how their equilibrium changes during chronic kidney disease (CKD). When the estimated GFR (eGFR) is < 60 mL/min/1.73 m2, the levels of PTH usually rise. After that, the eGFR drops to about 20 mL/min/1.73 m2, while serum calcium and phosphate concentrations stay within the normal range. Instead of renal tissue loss, an elevated FGF23 concentration causes the calcitriol concentration to drop substantially earlier, at a time when the eGFR is less than 60 mL/min/1.73 m2. [70]

By inhibiting the 1-α-hydroxylase enzyme, hyperphosphatemia also plays a role in the reduction of calcitriol synthesis. This eventually results in a lack of calcitriol and fuels the emergence of hypocalcemia.

Subsequently, these metabolic alterations trigger the release of Parathyroid hormone and elevate its levels through many mechanisms described below:

- Phosphate retention: Through several different pathways, serum hyperphosphatemia can induce PTH secretion. This usually happens through two different mechanisms: either PTH messenger ribonucleic acid levels are raised directly, or PTH levels are raised indirectly by lowering calcium and calcitriol levels. [71,36]
- Calcium: Calcium has a key role in controlling PTH levels via the CaSR. The known correlation between calcium and PTH levels is highlighted by the fact that a drop in serum calcium levels causes the parathyroid glands to release PTH.
- Calcitriol: Maintaining blood calcium levels and controlling PTH production are two important functions of calcitriol. To raise blood calcium levels, PTH and calcitriol combine. PTH secretion reflexively increases when calcitriol levels fall because of decreased intestinal absorption of calcium, which might result in secondary hyperparathyroidism. Furthermore, the parathyroid glands need calcitriol to inhibit the release of PTH.
- Fibroblast growth factor-23: The body's phosphate levels are lowered by FGF23. Reduced α-Klotho, also known as Klotho, is a transmembrane receptor mostly present in the proximal and distal renal tubules and is the first biochemical anomaly observed in chronic kidney disease (CKD). Reduced levels of Klotho, a cofactor for FGF23, result in increased FGF23 since there is no negative feedback. Through the sodium-phosphorus type II cotransporter, this rise in FGF23 causes a reduction in the reabsorption of phosphorus in urine. Furthermore, FGF23 inhibits the 1-α-hydroxylase enzyme, resulting in a reduction in activated vitamin D. [53,72]

PHOSPHATE RETENTION: There are several potential theories for phosphate retention in CKD, with the "trade-off" concept being one of them. According to this theory, calcitriol production is inhibited and the concentration of ionized calcium is lowered, which leads to secondary hyperparathyroidism. [73] Because of the decreased proximal tubular phosphate reabsorption, the ensuing excess of PTH encourages renal phosphate excretion. This process raises blood calcium levels by increasing bone resorption and boosting kidney calcitriol production, which improves intestinal calcium absorption. [74]

According to this theory, there are advantages to the initially adaptive rise in PTH, including decreased plasma phosphate concentration, decreased phosphate reabsorption, and enhanced phosphate excretion. Furthermore, it usually corrects hypocalcemia and calcitriol insufficiency. Overexposure to PTH, however, eventually has maladaptive long-term effects. Additionally, when CKD progresses, the compensatory increase in PTH is no longer enough, which keeps phosphate concentrations from falling. [75,76]

When individuals with CKD-MBD have hyperphosphatemia, the following pathogenic consequences occur:

1. Production of FGF23, which inhibits PTH secretion [77]
2. Circulatory calcification and arterial stiffness are caused by the osteoblastic transition of smooth muscle cells in the vasculature. [78]

DECREASED CALCITRIOL ACTIVITY:

The concentration of plasma calcitriol often drops when the eGFR is less than 60 mL/min/1.73 m2. This decline is mostly caused by the higher concentration of FGF23 in the early stages of the illness. However, decreased production of calcitriol is also a result of hyperphosphatemia and the shrinkage of working kidney mass in severe chronic kidney disease (CKD). decreased production of calcitriol results from FGF23 stimulating the 24-hydroxylase enzyme and suppressing the activity of 1-α-hydroxylase. [79]

The different CKD-MBD, such as phosphate, calcium, PTH, FGF23, and Klotho, depend on calcitriol. PTH may be impacted by decreased calcitriol activity in the following ways:

- Decreased intestinal calcium absorption
- Reduction in the parathyroid cells' vitamin D receptor count
- Elimination of the suppressive influence on the parathyroid gland [80]

DISORDERS OF CALCIUM BALANCE: PTH production is crucially regulated by calcium, which is plentiful in parathyroid glands and whose levels in the serum can fluctuate even little. The CaSR recognizes this. [81] In response to variations in ionized calcium concentrations, the CaSR tightly controls PTH production, with PTH secretion being inversely correlated with blood calcium levels. Patients with CKD are more likely to die from both hypocalcemia and hypercalcemia. [82] In chronic kidney disease (CKD), hypocalcemia is common and causes excessive PTH production (as detected by the CaSR), which in turn causes aberrant bone remodeling on the other hand, hypercalcemia is associated with extra-skeletal calcification.

FIBROBLAST GROWTH FACTOR-23: The key regulator of PTH levels is FGF23, whose levels increase even before an increase in PTH. [69] In reaction to calcitriol, dietary phosphate load, calcium, and PTH, FGF23 is released. [83] Due to reduced clearance, patients with CKD may also have elevated FGF23 concentrations. [84] By reducing renal phosphate reabsorption via the sodium/phosphorus cotransporter type II and blocking intestinal phosphate absorption through reduced calcitriol synthesis, FGF23 maintains appropriate serum phosphate levels. Moreover, FGF23 suppresses 1-α-hydroxylase expression in the proximal tubule, which reduces the production of calcitriol. [85] Lower blood phosphate levels result from these activities, enhancing urine phosphate excretion and decreasing intestinal phosphate absorption. In addition, FGF23 inhibits the parathyroid gland's production of PTH. [86]

The transmembrane protein klotho in both the proximal and distal renal tubules is essential for FGF23 receptor activation [87] Additionally, Klotho may regulate bone mass and development. There is a feedback loop between FGF23 and Klotho, where low 1, 25-dihydroxy vitamin D levels in Klotho insufficiency cause raised FGF23 levels, and increasing FGF23 concentrations worsen Klotho deficiency. [88]

➢ EVALUATION: DIAGNOSTIC APPROACHES FOR CKD-MBD

When clinical suspicion is strong, an examination should be conducted because the majority of people with CKD-MBD are asymptomatic at the onset of the illness. Despite being the gold standard for diagnosis, a bone biopsy is intrusive and not always practical. Nonetheless, radiographic imaging in conjunction with blood testing for bone metabolism indicators can aid in narrowing the differential diagnosis in the individuals listed below.

- PTH can distinguish between states with high and low bone turnover, and it is important in the pathophysiology of CKD-MBD. [38] Whether or not a patient receives dialysis affects the diagnostic threshold level for PTH.
- The next logical step would be to measure blood levels of vitamin D if PTH is excessive.
- The diagnosis of CKD-MBD is mostly dependent on serum calcium and phosphate levels.
- BSALP, a protein unique to bones, is a marker of osteoblast activity. A low bone turnover condition may be suggested by low BSALP levels, which would help with diagnosis.
- Renal osteodystrophy patient's blood contains indicators of bone production, such as osteocalcin and pro-peptides of type I collagen. Nevertheless, they are not frequently utilized in clinical practice because of a weak correlation with the condition in research findings. [71]

When describing bone disease linked to CKD-MBD, radiological examinations are essential. Skeletal alterations suggestive of underlying renal osteodystrophy are a symptom of osteitis fibrosa associated with hyperparathyroidism. The clavicle, distal phalanges, and cranium may exhibit osteolysis, subperiosteal resorption, and endosteal resorption. Bone mineral density is measured using dual-energy x-ray absorptiometry (DEXA) scans, although it's not yet clear if these tests are truly validated.[89] In patients with CKD who have osteoporosis risk factors, the 2017 KDIGO guideline suggested using bone mineral density testing to assess fracture risk and make necessary therapeutic modifications depending on the findings.

A bone biopsy and double tetracycline labelling are the final tests used to diagnose CKD-MBD since they precisely determine the patient's histological pattern of bone disease. [41] FGF23 is another newly discovered marker that has drawn interest lately. Due to issues including instability (ex vivo degradation), diurnal fluctuation, high cost, and lack of accuracy, FGF23 is rarely used as a biomarker, despite its well-established clinical benefits. [90]

- **MONITORING PARAMETERS:**

Serum levels of PTH, calcium, and phosphate are routinely measured in patients with secondary hyperparathyroidism. [91] To determine whether a parathyroidectomy is necessary, some medical professionals additionally incorporate BSALP into their monitoring regimen. Still, there isn't enough data to adequately justify its use. Even though PTH and BSALP may separately indicate high-turnover bone disease on their own, their combined usage adds nothing to the predictive power of the test. [92]

There is no standard monitoring frequency for CKD-MBD. It is generally considered suitable to measure blood phosphate and calcium levels every one to three months and PTH every three to six months. [91] These intervals might be changed, though, if therapeutic modifications are made that could affect these levels. A lot of medical professionals choose to take yearly measurements of vitamin D levels.

- **TREATMENT / MANAGEMENT**

The degree of the underlying renal impairment, the predominant metabolic abnormalities, and the distinctive bone disease all influence the treatment plan for individuals with CKD-MBD. PTH, calcium, vitamin D, and phosphate hormone levels must all be closely monitored to treat this illness.

- **TREATMENT FOR ADULT NON-DIALYSIS PATIENTS:**

Secondary hyperparathyroidism can occur in any patient with chronic kidney disease (CKD) and an eGFR of less than 60 mL/min/1.73 m2. Thus, it is advised to monitor 25-hydroxy vitamin D, BSALP (when available), PTH, calcium, phosphate, and so on. Treatment is guided by the ongoing evaluation of these biochemical indicators. For patients who are not receiving dialysis, a management plan could consist of the following elements:

- **Hyperphosphatemia:** To lower increased PTH levels, serum phosphate levels must be kept at 5.5 mg/dL. Because vegetarian proteins have a reduced bioavailability of phosphorus, patients are strongly urged to adopt a phosphorus-restricted diet, with preference given to vegetarian meals. [93] Phosphate binders should be administered with meals for patients whose blood phosphate levels remain elevated after following dietary guidelines. Since they don't alter calcium levels, non-calcium-containing binders like lanthanum and sevelamer are recommended. [94]
- In the past few decades studies were done on sevelamer carbonate role in CKD-ND patients with hyperphosphatemia **- Ketteler, Markus & Rix et al.** [122] did a study (2007) on the enhanced, buffered version of sevelamer hydrochloride called sevelamer carbonate to treat hyperphosphatemia in individuals with chronic kidney disease. This study looked at sevelamer carbonate's capacity to regulate serum phosphorus in hyperphosphatemic individuals with chronic renal disease who weren't receiving dialysis. This was a dosage-titration, open-label trial. They recruited patients (n = 46) whose serum phosphorus level was greater than

5.5 mg/dl. For eight weeks, sevelamer carbonate was administered. Native vitamin D (400 IU) was given to the patients as a supplement. The change in serum phosphorus from baseline was the main effectiveness metric. The secondary measures were the percentage of serum phosphorus responders, variations in bicarbonate, calcium-phosphorus product, and serum lipids, as well as safety and tolerability. The mean serum phosphorus levels decreased statistically significantly from baseline to the completion of the sevelamer carbonate treatment. After treatment, 75% of patients with stage 4 chronic kidney disease and 70% of patients with stage 5 chronic kidney disease reached the target serum phosphorus. After the treatment, there were statistically significant increases in mean blood bicarbonate levels (from 16.6 to 18.2 mEq/L) and statistically significant decreases in serum calcium-phosphorus product, total cholesterol, and low-density lipoprotein cholesterol. The sevelamer carbonate was accepted effectively. For hyperphosphatemic patients with chronic kidney disease who do not undergo dialysis, sevelamer carbonate is a safe, effective treatment for controlling their phosphorus levels.

- **Vincenzo Savica et al.** [123] In 2008 conducted research on the use of sevelamer carbonate to treat hyperphosphatemia in patients receiving hemodialysis for chronic renal disease. When a phosphate molecule develops an ionic or hydrogen bond with sevelamer hydrochloride, a non-metal, non-calcium quaternary amine anion exchange resin, one hydrochloride molecule is released. Sevelamer hydrochloride has been found to worsen the metabolic acidosis that HD patients suffer for the reasons mentioned above. As a result, serum bicarbonate thresholds of 17–19 meq/L are observed, which is lower than the recommended K/DOQI level of 22 meq/L. Anion substitute prescription drugs Sevelamer hydrochloride, which is not absorbable, was improved by creating sevelamer carbonate. With an actual daily dosage of 5.5 g (6–7 sevelamer carbonate 800 mg tablets), sevelamer carbonate was administered to CKD patients who were not undergoing renal

replacement therapy and had mean serum P levels of 6.2 ± 0.8 mg/dl. An 8-week therapy period that included a notable 1.4 mg/dl drop in serum phosphorus was followed by a 2-week washout period for patients who had previously taken any other phosphate binders, especially calcium-based phosphate binders. After therapy, serum phosphorus completely returned to baseline levels after a two-week washout period. By the end of the sevelamer carbonate treatment, 75% of stage 4 CKD patients (GFR 15–29 ml/min per 1.73 m2; 35% of the study population) had reached a serum phosphorus level ≤5.5 mg/dl, and 70% of stage 5 CKD patients (GFR < 15 ml/min per 1.73 m2; 65% of the study population) fell into the K/DOQI recommended range of ≥2.7 and ≤4.6 mg/dl.

- **Chen, Nan, and Wu et al.** [124] Did a study in 2013 on individuals with advanced chronic kidney disease (CKD) with hyperphosphatemia which is linked to unfavourable consequences such as increased death rates and vascular calcification. The effectiveness and safety of phosphate binders in a modern cohort of Chinese hemodialysis patients—who differ genetically and dietically from other populations—have not previously been documented, even though phosphate reduction is a crucial part of the management of chronic kidney disease. Furthermore, little information is currently available regarding the best ways to titrate dosages when switching from a polymer-based phosphate binder to one based on calcium. In this 8-week, randomised, double-blind dose-titration research, Chinese CKD patients receiving hemodialysis were compared with a placebo and sevelamer carbonate (initial dose: 800 mg, three times daily). Before the research began, patients had to take calcium-based binders. A total of 205 patients were randomly assigned (n = 135 for sevelamer and 70 for placebo); their mean age was 48.6 years, 61% of them were men, and their mean dialysis duration was 4.4 years. With sevelamer carbonate treatment, the mean serum phosphorus dramatically decreased (change = −0.69 ± 0.64 mmol/L (−2.14 ± 1.98 mg/dL)) but remained chronically elevated (change = −0.06 ±

0.57 mmol/L (−0.19 ± 1.76 mg/dL)) with placebo. (P < 0.0001). Sevelamer carbonate therapy produced statistically significant larger mean baseline decreases in low-density lipoprotein cholesterol (−33.5 versus −7.6%) and serum total cholesterol (−17.1 against −3.3%) when compared with placebo (P < 0.0001 for both). In comparison to the placebo arm, which had 97% adherence, sevelamer carbonate had a 96% adherence rate, indicating good tolerance. Patients in the sevelamer carbonate and placebo therapy groups often reported side events that were comparable to each other and related to their underlying renal illness. This study showed that in end-stage CKD patients receiving a placebo, hyperphosphatemia persistently elevated and rapidly developed when phosphate binders were stopped. In modern Chinese hemodialysis patients, gradually increasing SC from a starting dose of 2.4 g/day to a daily dose of 7.1 ± 2.5 g/day was well tolerated, effective, and safe.

- But medical professionals may also recommend calcium-containing binders like calcium carbonate and acetate when patients have hypocalcemia and need calcium supplementation. Furthermore, it is crucial to guarantee that, under these circumstances, elemental calcium consumption does not exceed 2 g/d. [95]
- **Calcium:** Calcium or vitamin D derivatives, such as calcitriol or synthetic vitamin D analogues, are usually not necessary for the treatment of asymptomatic patients with moderate hypocalcemia (above 7.5 mg/dL with normal albumin levels). Hypercalcemia or a positive calcium balance may result from certain therapies. Mitigating vitamin D insufficiency has the potential to indirectly rectify moderate hypocalcemia.

The increased risk of vascular calcification is a further issue with the oral administration of calcium and vitamin D analogues. While 1000 mg of calcium should be consumed daily through food, a prescription 1500 mg of elemental calcium (calcium carbonate, 1250 mg thrice a day) boosts calcium intake by roughly 2.5 times. When combined with

decreased calcium excretion in chronic kidney disease (CKD), this leads to a positive calcium balance, which further encourages vascular calcification and other problems. [96]

- **Vitamin D:** Vitamin D insufficiency is common in people with chronic kidney disease (CKD) and might appear as a first-test anomaly. This nutrient is associated with hyperparathyroidism and may make hypocalcemia worse.
- Except in the following circumstances, cholecalciferol or ergocalciferol supplements are usually given to CKD patients who are vitamin D deficient:
    - Until their phosphate levels are under control, patients with hyperphosphatemia
    - Individuals who are hypercalcemic

Patients with advanced hyperparathyroidism are the only ones eligible for activated vitamin D (calcitriol). In CKD patients, the efficacy of vitamin D therapy is still debatable. [97] Vitamin D supplementation has been shown in a meta-analysis to increase PTH and vitamin D levels, which may help to lower the risk of hyperphosphatemia and hypercalcemia. [98]

- **Hyperparathyroidism:** Aiming to address modifiable risk factors such as vitamin D insufficiency, hyperphosphatemia, and excessive phosphate consumption, patients with chronic kidney disease (CKD) with persistent or progressive hyperparathyroidism should get therapy. One option is to use calcitriol if these methods are not successful in lowering PTH levels. PTH levels have been shown to decrease or stabilise with calcitriol and synthetic vitamin D analogues (occasionally with a risk of producing hypercalcemia). [99,100] Healthcare professionals may decide to start calcitriol or synthetic vitamin D analogues at different periods. Generally, though, therapy starts when PTH levels are two to three times higher than the upper limit (for example, 150–200 pg/mL if the upper limit is 65 pg/mL). Starting at 0.25 µg, three times a week, is

the suggested dosage, with titration needed to reach a target PTH level below 150 pg/mL.

When the free calcium concentration is 9.5 mg/dL (2.37 mmol/L) or above, or when phosphate levels are above normal, calcitriol should not be used. Many oral medications, including doxercalciferol, paricalcitol, alfacalcidol, and calcitriol, can be regarded as having comparable efficacy in patients who do not get dialysis. [101]

Calcimimetics, like cinacalcet, belongs to another class of pharmaceuticals. For individuals who are not receiving dialysis, this class is not advised for PTH suppression. Its usage in individuals not receiving dialysis is complicated by several side effects, such as hyperphosphatemia, elevated calciuria, and hypocalcemia. [102]

Regarding cinacalcet, the KDIGO 2017 advice makes no particular recommendations. Due to a lack of data in CKD patients undergoing predialysis, previous KDIGO recommendations recommended against using cinacalcet. [103]

- **TREATMENT FOR ADULT DIALYSIS PATIENTS**

Dialysis patients should aim for the following therapeutic goals:

• For dialysis patients, phosphate levels should normally be between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L).

• The optimal range for serum calcium levels is less than 9.5 mg/dL or 2.37 mmol/L.

• PTH levels are to be kept between two and nine times the assay's upper limit. [104]

After hyperphosphatemia is under control, trends, as opposed to individual test readings, are used to manage PTH. Specifically, because it can result in adynamic bone disease, it is not recommended to reduce PTH to less than twice the maximum limit. [103]

- **hyperphosphatemia:** treatments for high PTH might be complicated by excessive phosphate levels since they may cause serum phosphate levels to rise. Therefore, phosphate management is essential for individuals with chronic hyperphosphatemia greater

than 5.5 mg/dL. Given that blood phosphate has been linked to mortality in dialysis patients, treatment should start if the level is higher than 5.5 mg/dL (1.78 mmol/L). [105] Phosphate limitation and the usage of phosphate binders are common first tactics. [106] Nonetheless, it is advised to limit phosphate consumption through diet to 900 mg/d; this should be monitored by a dietitian, particularly since many dialysis patients suffer from overt or mild malnourishment. Most patients with increased phosphate levels require both phosphate binder drugs and dietary modifications, which is why doctors usually start both methods for patients with hyperphosphatemia.

There are two types of phosphate binders: those that contain calcium and those that do not. Calcium-containing binders comprise calcium acetate and carbonate, whereas non-calcium-containing binders include sevelamer and lanthanum. Other alternatives include ferric citrate and sucroferric oxyhydroxide, both of which are as effective in reducing phosphate. [95] In the past few decades, studies were done on ferric citrate role in CKD-DD patients with hyperphosphatemia - **Glenn M. Chertow et al.** [125] did a study (2017) on patients with iron deficiency anaemia, who are not on dialysis and are known case of chronic kidney disease, with normal or raised levels of phosphorus. Two randomized, placebo-controlled trials indicated that FC significantly raised the levels of haemoglobin and reduced serum phosphate levels. analysing these trials results could find a more thorough assessment of ferric citrate's safety and efficacy in this group, after pooling the outcomes of phase 2 (n = 149) and 3 trials (n = 233) of patients randomised and prescribed up to 12 and 16 weeks, respectively. The intial dose in above two trials was thrice 1-g (elemental iron 210 mg) pills per day with meals, up to 12 pills/day. Doses were titrated in the trial phases 2 and 3 to reduce serum phosphate levels to a target levels (0.97–1.13 mmol/L) and to reach levels of more than 10 g/L haemoglobin, respectively. Safety was checked in all patients who were prescribed 1 dose of FC (n = 190) and a placebo (n = 188). Treatment-related adverse effects (AEs) were

seen in 143 of 190 (75.3%) FC-prescribed and 116 of 188 (61.7%) placebo-prescribed patients; GI- AEs were the most common (94 [49.5%] vs. 52 [27.7%], respectively). A significant adverse effect (AE) occurred in 20 patients prescribed with FC (10.5%) and 21 patients prescribed with placebo (11.2%). In both groups, there were two (1.1%) mortality. Serum phosphate reduced mildly and haemoglobin increased, with mild deviations from the normal levels, according to a pooled efficacy results. While FC also corrects two of the primary metabolic complication of CKD (iron-deficiency anaemia and relative hyperphosphatemia), it also causes gastrointestinal adverse effects (AEs) more than placebo in patients with NDD-CKD.

Geoffrey A. Block et al. [126] Did a study (2018) on people with advanced CKD with anemia and CKD-related anomalies in mineral metabolism, such as phosphate and FGF23 abnormalities. To find out the potential beneficial effects of fixed-dose FC coordination complex on various biochemical parameters in patients with advanced CKD, they randomly allocated 203 patients with eGFR<20 ml/min per 1.73 m2 2:1 to either usual care or a fixed dose of FC coordination complex (210 mg ferric iron per tablet, two tablets per meal) for nine months or until three months after beginning dialysis. The baseline characteristics of the two groups were similar overall, with the usual-care group having a higher prevalence of diabetes and peripheral vascular disease. In addition to drastically lowering serum phosphate and intact FGF23, the FC coordination complex also markedly enhanced haemoglobin, transferrin saturation, and serum ferritin (P - 0.001 for all). Similar to the 32 of 66 (48%) patients randomised to usual treatment, 31 (23%) of the 133 patients assigned to the FC coordination complex started dialysis throughout the trial period (P = 0.001). FC coordination complex therapy substantially reduced annual hospital admissions, days in the hospital, and the composite end outcome of mortality, dialysis, or transplantation compared to standard care (P = 0.002). The excellent safety profile of a fixed-dose ferric citrate coordination complex in an unselected population with advanced chronic kidney disease (CKD) is supported by its beneficial effects on biochemical

parameters and the exploratory results regarding hospitalisation and the composite endpoint. These findings warrant further research in the same drug category.

Peter A. Mccullough et al. [127] Did a study (2018) on Iron deficiency anaemia (IDA) in undertreated patients of chronic inflammatory diseases, such as heart failure (HF) and chronic kidney disease (CKD). CKD- and HF-related progressive inflammation and decreased iron transport may make oral iron therapy less effective. In individuals with CKD, oral ferric citrate improves anaemia indicators; however, its effects in patients with concomitant HF are unknown. Ferric citrate (n = 190) or a placebo (n = 188) was administered to CKD patients who did not receive dialysis and iron supplements for IDA from phase 2 and 3 trials; individuals with HF were identified based on their medical histories. A haemoglobin increase of more than 10.0 g/L was called the haemoglobin response. Haemoglobin, ferritin, serum phosphate, transferrin saturation, and changes from baseline to week 12 were assessed, as was the frequency of adverse events that might be associated with heart failure. Of the patients, 22% (n = 81) had a history of HF. Patients with or without HF did not substantially differ in the group responding to ferric citrate treatment (43% vs. 49%, respectively; p = 0.47); changes from baseline in haemoglobin, iron parameters, and serum phosphate were comparable. Individuals with HF had a higher frequency of adverse events (FC, 23%; placebo, 17%) compared to individuals without HF (FC, 12%; placebo, 11%) that may be associated with heart failure. In the end, these findings suggest that ferric citrate may have a place in managing IDA in individuals with concurrent heart failure who do not receive dialysis.

For the majority of patients, binders free of calcium are usually preferable. In some situations, however, such as when adjunct calcimimetic medication is being used and non-calcium binders are impractical or unavailable, or when hypocalcemia and hyperparathyroidism are present, calcium-containing binders might be taken into consideration. However, several professionals advise against using calcium-containing binders regularly. [91]

Phosphate removal is limited by normal 4-hour dialysis procedures, which remove an average of 900 mg of phosphate each session and must be done three times a week.

- **Calcium:** It is crucial to keep calcium levels below 9.5 mg/dL (2.37 mmol/L). Because there is a chance of hypercalcemia, asymptomatic and moderate hypocalcemia do not need to be treated. By varying the calcium content in the dialysate, dialysis patients' calcium levels are kept close to the upper end of the normal range. This lowers the calcium and phosphorus (Ca and P) product and suppresses PTH. Increased mortality and increasing hyperparathyroidism are linked to hypocalcemia. [107]

For individuals with poor bone turnover conditions, a different strategy is used. Lowering calcium and vitamin D levels is an attempt to avoid PTH suppression. PTH suppression is avoided by using non-calcium-containing binders, which raise phosphate levels without increasing calcium levels. This approach has been demonstrated to accelerate the production of new bone. [108] For similar reasons, the calcium content in the dialysate is likewise maintained below normal levels. But it's still unclear what the benefits of cutting back on or eliminating vitamin D consumption are.

- **Vitamin D:** Treating vitamin D insufficiency is essential since low vitamin D levels have been linked to a higher risk of death in hemodialysis patients. [109] Ergocalciferol and cholecalciferol both work well to raise vitamin D levels. [110]
- **Hyperparathyroidism:** For the treatment of hyperparathyroidism, calcimimetics, calcitriol, synthetic vitamin D analogues, or a mix of the two can be used to lower PTH levels.

If PTH levels are extremely high, these medicines are inadequate when used alone, thus a combination is usually needed. [111] If calcium levels are above 10.2 mg/dL or phosphate levels exceed 5.5 mg/dL, calcitriol or synthetic vitamin D analogues are stopped or given at a reduced dosage. [112] The patient may start taking cinacalcet or resume these medications at half the dose if the hyperphosphatemia or

hypercalcemia has subsided. Usually, a modest dosage of 0.25 µg is administered three times a week to commence calcitriol or vitamin D analogues. Usually, within the first three to six months of therapy, the response can be shown; if needed, dose changes can be done every four to eight weeks. [113]

Because calcimimetics increases CaSR's sensitivity to calcium, serum PTH levels are lowered, which in turn lowers calcium and phosphate levels.[114] There are two commonly used calcimimetics: etelcalcetide (intravenous) and cinacalcet (oral), with etelcalcetide being used for refractory patients. It is more likely to reach goal PTH levels with calcimimetics in combination with continued calcitriol or vitamin D analogues and phosphate binders without producing hyperphosphatemia or hypercalcemia. [115]

Moreover, cinacalcet lessens the need for a parathyroidectomy. [116] However, parathyroidectomy may be more successful than cinacalcet, especially for those with extremely high PTH levels, as cinacalcet has not been shown to lower death rates. [116] Depending on a patient's calcium and phosphate levels, there have historically been two ways to treat them; clinicians usually select a course of action depending on their training and the available information.

The 2017 KDIGO recommendations advise using the subsequent method:

- Lower blood calcium levels than 9.5 mg/dL (2.37 mmol/L) and lower serum phosphate levels than 5.5 mg/dL (1.78 mmol/L): Initial treatment for these individuals is calcitriol monotherapy. Raising the calcitriol dosage to reach target PTH levels while maintaining serum phosphate levels below 5.5 mg/dL is the aim of the treatment. If the desired PTH levels are not attained, cinacalcet may be started (provided that the calcium concentration is greater than 8.4 mg/dL). Usually starting at 30 mg/d, the dosage of cinacalcet is gradually increased to 60, 90, and 180 mg/d as needed.
- Levels of serum calcium over 9.4 mg/dL (2.37 mmol/L) or phosphate above 5.4 mg/dL (1.78 mmol/L): Cinicalcet should be

started before calcitriol or other synthetic analogues in individuals with these excessive levels and consistently high PTH despite maximum phosphate-reducing treatment. When calcium levels are less than 8.4 mg/dL (2.1 mmol/L), the use of cenacalcet should be avoided because of the possibility of hypocalcemia. When phosphate and calcium levels are below 5.5 mg/dL (1.78 mmol/L) and 9.5 mg/dL (2.37 mmol/L), respectively, the patient may be evaluated for calcitriol or synthetic vitamin D analogues if goal PTH levels are not satisfied.

➢ DIFFERENTIAL DIAGNOSIS

Patients exhibiting indications of structural abnormalities or bone disease are evaluated using PTH, alkaline phosphatase, calcium, and phosphate levels. While a history of chronic kidney disease (CKD) may indicate CKD-MBD, it is important to rule out other bone illnesses, including:

- Osteopenia,
- Osteoporosis
- Vitamin D-Resistant Rickets
- Osteopetrosis
- Bone Paget Disease

for a proper diagnosis and course of treatment.

➢ PROGNOSIS

Numerous investigations have been carried out in an attempt to link death rates in people with chronic kidney disease (CKD) with abnormal mineral metabolism. A direct and independent correlation was shown between aberrant mineral metabolism (serum PTH, phosphate, vitamin D, calcium, and calcium-phosphorus product) and all-cause and cardiovascular mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). [117] Studies have looked at the relationship between hyperphosphatemia and higher mortality, especially in non-dialysis CKD patients. According to a noteworthy meta-analysis

including over 5,000 CKD patients, there is a 35% increase in mortality for every milligram that blood phosphate rises above the normal range. [105]

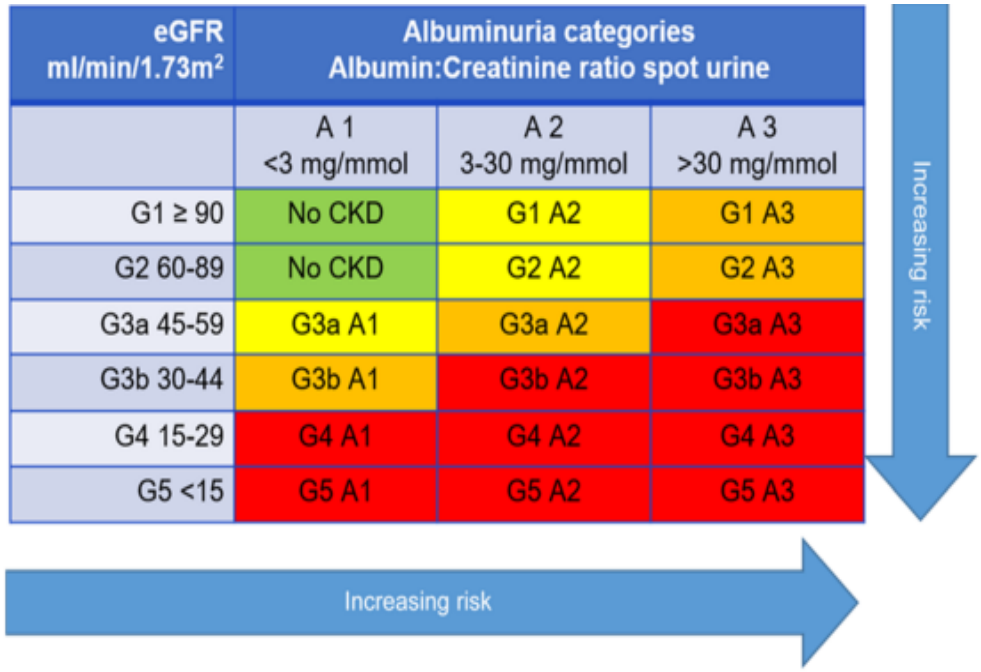
Typically, a kidney transplant is necessary to fully recover from renal osteodystrophy. But it's important to take into account other aspects, such as the bone-vascular axis when evaluating the overall prognosis of this disorder. This axis includes cardiovascular events that follow in individuals with renal osteodystrophy, vascular calcifications, and blood vessel arteriosclerosis. The prognosis for people with this illness depends critically on comprehending and treating these interrelated elements. [118]

- **COMPLICATIONS**

A complication of CKD is CKD-MBD. When mineral bone disease progresses, patients frequently have skeletal abnormalities, bone pain, and growth retardation in younger kids. The progressive decline in cardiac parameters, such as vascular calcification and cardiac remodelling, is another important consequence of CKD-MBD. However, QT prolongation brought on by CKD-MBD medication, such as reduced calcium dialysate and calcimimetics, might result in deadly arrhythmias. Unusual cardiac events that can be classified as a component of the CKD-MBD-specific cardiac complex syndrome include sudden cardiac death and heart failure brought on by severe arrhythmias. [119]

Research has demonstrated that individuals with an initial fragility fracture history and renal osteodystrophy are at an increased risk of developing metastatic calcification and cardiovascular events. [120] Moreover, CKD-MBD may be linked to consequences including an elevated risk of hemorrhagic stroke, muscular weakness, increased infections, and arrhythmias

FIGURE 1: NICE/KDIGO classification of CKD using eGFR and ACR categories [121]



eGFR ml/min/1.73m²	Albuminuria categories Albumin:Creatinine ratio spot urine		
	A 1 <3 mg/mmol	A 2 3-30 mg/mmol	A 3 >30 mg/mmol
G1 ≥ 90	No CKD	G1 A2	G1 A3
G2 60-89	No CKD	G2 A2	G2 A3
G3a 45-59	G3a A1	G3a A2	G3a A3
G3b 30-44	G3b A1	G3b A2	G3b A3
G4 15-29	G4 A1	G4 A2	G4 A3
G5 <15	G5 A1	G5 A2	G5 A3

MATERIALS AND METHODS

This was a prospective observational study that was conducted at Dayanand Medical College and Hospital, Ludhiana, Punjab, India. Including Patients with Non-Dialysis Dependent Chronic Kidney Disease Stages III–V (According to KDIGO Classification) over 12 Months, Including 3 Months of Short-Term Follow-Up on 100 patients.

SELECTION OF PATIENTS FOR STUDY:

INCLUSION CRITERIA: All patients having chronic kidney disease between stage - III to V non-dialysis by KDIGO (kidney disease improving global outcome) classification with Hyperphosphatemia (>4.5) will be included in the study.

EXCLUSION CRITERIA: Patients with chronic kidney disease stage I, II, and V dialysis dependent by KDIGO (kidney disease improving global outcome) classification will be excluded from the study.

MATERIALS AND METHODS: During the study period, all 100 patients fulfilling the KDIGO (kidney disease improving global outcome) classification with Hyperphosphatemia (>4.5) were included and studied over 12 months. Written performas were filled out during admission which contained epidemiological information (age, sex, address), and chief complaints (shortness of breath, pedal edema, reduced urine output, etc.). vitals were taken at admission or on opd visit. Baseline lab investigation was taken (serum creatinine, urine routine, and phosphorus). If eGFR falls under the inclusion category (KDIGO CKD III to V non-dialysis) and phosphorus is raised (> 4.5). other lab investigation was followed (serum haemoglobin, calcium, iron, TIBC, transferrin saturation, ferritin, alkaline phosphate, and parathyroid). After taking due consent patient was enrolled in the study and started on either ferric citrate or sevelamer carbonate. Follow-up is advised after 3 months, 6 months, and 12 months. On follow-up above lab parameters were repeated and parameters were compared between both groups for each patient.

OUTCOME: A decrease in phosphorus and change in renal function and anemia profile were studied in both groups.

TOOLS OF THE DATA COLLECTION: A self-drafted, pre-tested structured schedule was used as the main tool of data collection, and it was drafted based on variables to fulfil the objectives of the study.

STATISTICAL DATA: Continuous variables were described as median and interquartile range (IQR), and categorical variables as absolute frequencies and percentages. Data was presented graphically using bar charts and pie charts as needed. To apply the appropriate statistical test first, we checked the nature of the data whether it was normally distributed or not, for the Kolmogorov-Smirnov test or Shapiro-wilk test was used. To check the association between categorical variables, the Chi-square ($\chi 2$) test was used (fisher exact test if any of the expected frequencies is less than 5). Independent t-test (parametric) or Mann Whittney-U test (non-parametric) was used to compare the parameters. The results were considered statistically significant when the two-tailed p-value was less than 0.05. All statistical calculations will be done using (the Statistical Package for the Social Science) SPSS 26 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

THE PATIENTS UNDERWENT THE FOLLOWING INVESTIGATIONS:

1. Serum Iron Levels
2. Serum Total Iron Binding Capacity (TIBC)
3. Serum Transferrin Saturation Levels
4. Serum Ferritin Levels
5. Serum Haemoglobin Levels
6. Serum Phosphorus Levels
7. Serum Parathyroid (PTH) Levels
8. Serum Calcium Levels
9. Serum Alkaline Phosphate (ALP) Levels
10. Serum Bone Specific Alkaline Levels (If required)

OBSERVATIONS AND RESULTS

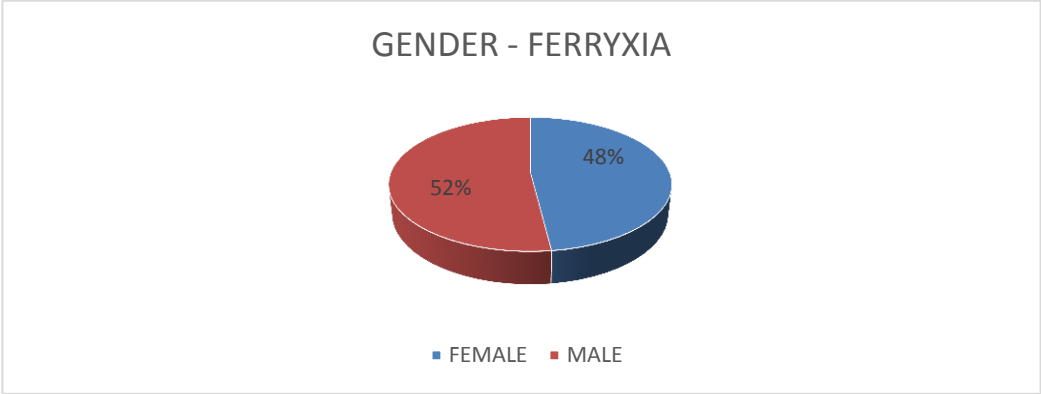
100 cases were enrolled and all were completed with the follow-up.

DEMOGRAPHIC CHARACTERISTICS

TABLE 4: GENDER-WISE DISTRIBUTION OF THE PATIENTS WITH CKD

Gender	FERRIC CITRATE N (%)	SEVELAMER CARBONATE N (%)
MALE	26 (52)	28(56)
FEMALE	24(48)	22(44)
Total	50 (100)	50(100)

In our study, out of 100 patients, 26 (52%) patients were males, 24 (48%) were females in the ferric citrate group, 28 (56%) patients were males and 22 (44%) were females in the sevelamer carbonate group.



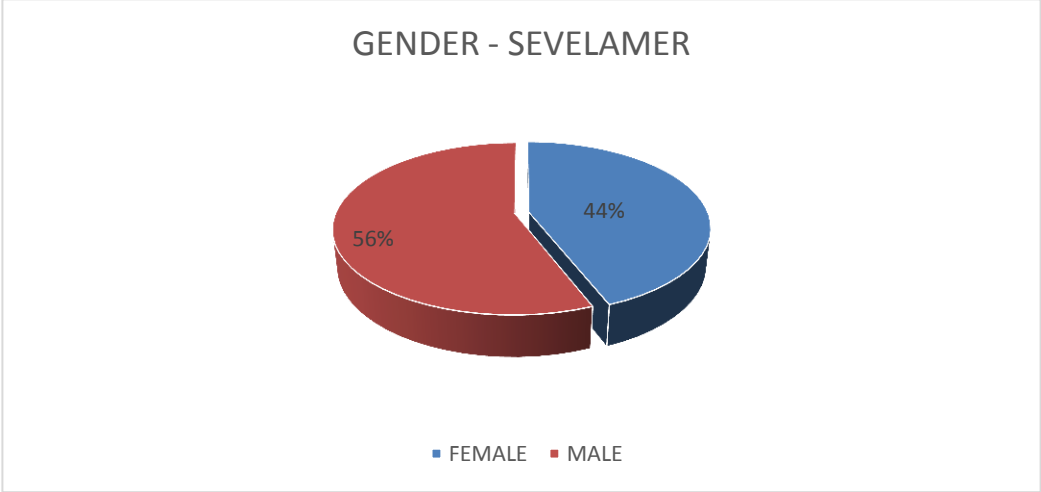


FIGURE 2: GENDER-WISE DISTRIBUTION OF THE PATIENTS WITH CKD IN BOTH GROUP

TABLE 5: KDIGO CKD CATEGORY-WISE DISTRIBUTION OF THE PATIENTS:

CKD CATEGORY	FERRIC CITRATE N (%)	SEVELAMER CARBONATE N (%)
CKD III	8 (16%)	5 (10%)
CKD IV	38 (76%)	39 (78%)
CKD V	4 (8%)	6 (12%)
Total	50 (100%)	50 (100%)

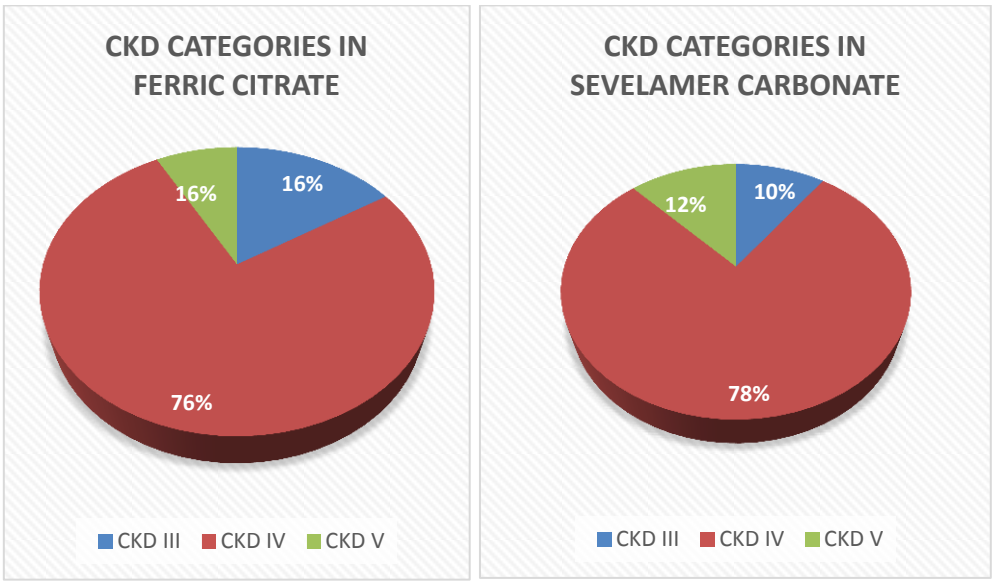


FIGURE 3: CATEGORY-WISE DISTRIBUTION OF THE PATIENTS WITH CKD

Most of the patients in the ferric citrate group were from CKD category IV (76%) followed by CKD III (16%) and CKD V (8%).

Most of the patients in the sevelamer carbonate group were from CKD category IV (78%) followed by CKD V (12%) and CKD III (10%).

TABLE 6: AGE DISTRIBUTION IN PATIENT WITH CKD IN BOTH GROUPS

AGE (YEARS)	FERRIC CITRATE N (%)	SEVELAMER CARBONATE N (%)
<20	1 (2)	1 (2)
20-40	8 (16)	5 (10)
41-60	22 (44)	23 (46)
>60	19 (38)	21 (42)
TOTAL	**50 (100)**	**50 (100)**

Most of the ferric citrate group patients were in the age group of >40 years (82%) and most of the sevelamer carbonate group patients were also in the same age group of >40 years (88%).

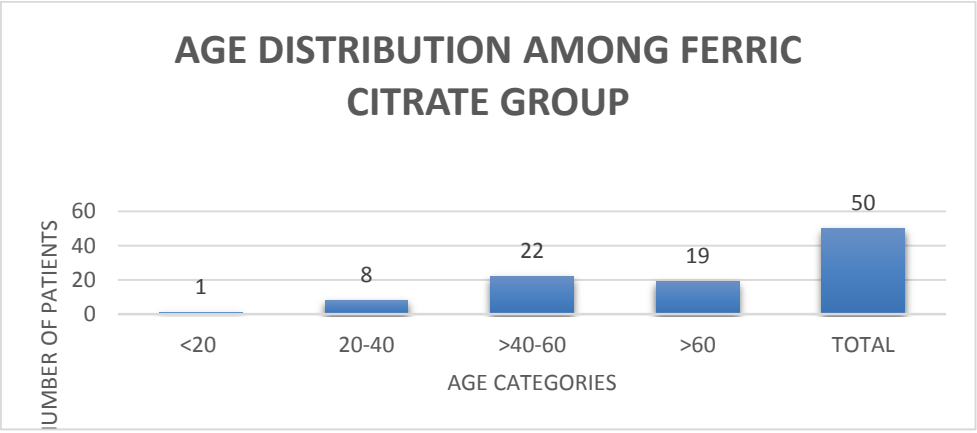


FIG 4A: AGE DISTRIBUTION AMONG FERRIC CITRATE GROUP

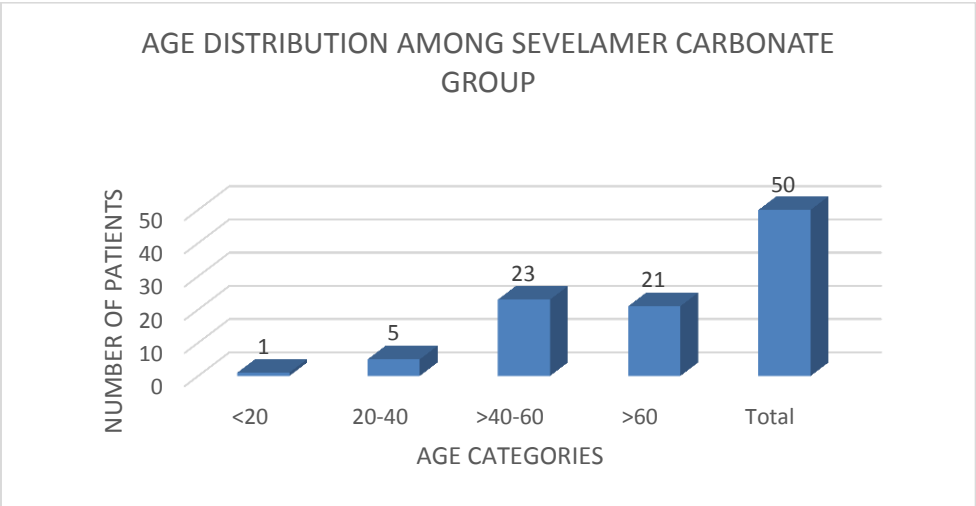


FIG 4B: AGE DISTRIBUTION AMONG SEVELAMER CARBONATE GROUP

TABLE 7: SERUM IRON IN PATIENTS OVER ONE YEAR IN EACH GROUP

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTHS	66.87	58.99
3 MONTHS	73.96	58.70
6 MONTHS	86.72	59.04
12 MONTHS	105.95	61.85

In the ferric citrate group mean serum iron increased from 66.87 (at 0 months) to 105.95 (at 12 months). In the sevelamer carbonate group, mean serum iron increased from 58.99 (at 0 months) to 61.85 (at 12 months).

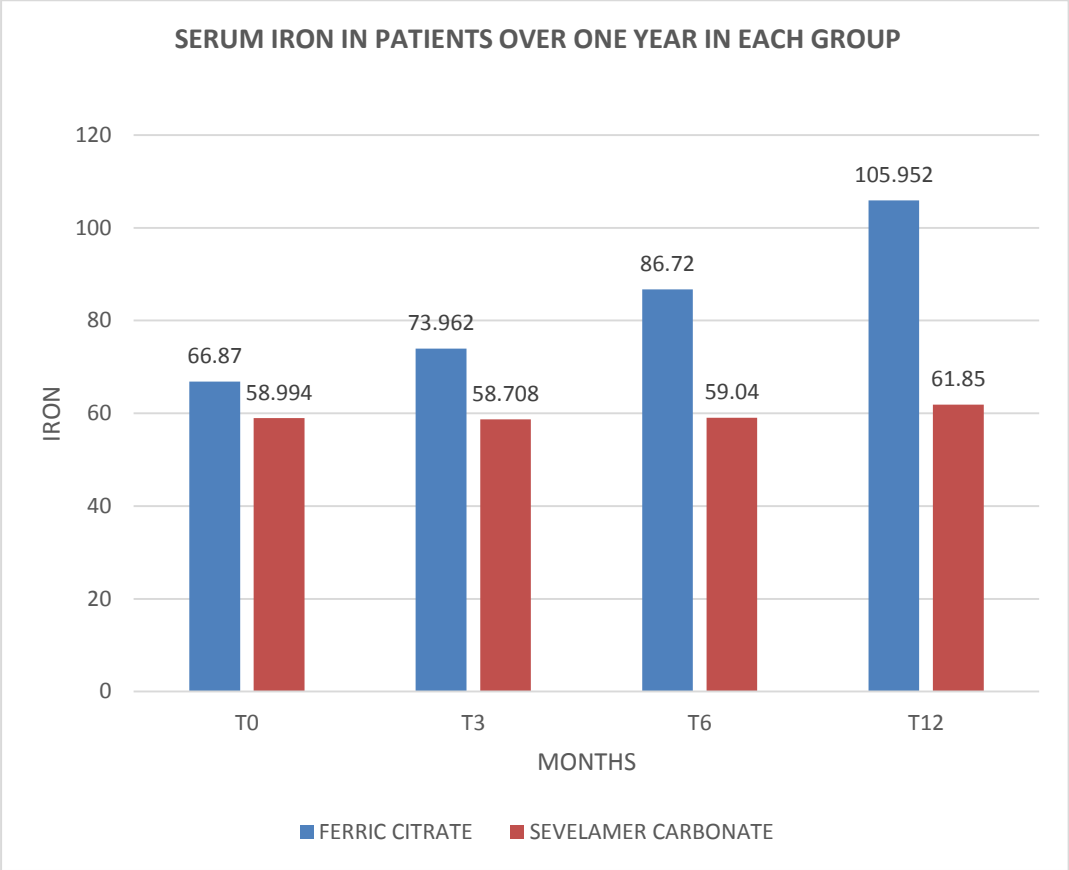


FIGURE 5: SERUM IRON IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 8: RESULTS OF SERUM IRON IN PATIENTS OVER ONE YEAR IN EACH GROUP:

GROUP	N	Mean rank	Sum of ranks	U value	P value	Effect size (R-value)
FERRIC CITRATE (O MONTH)	50	55.32	2766	1009.0	0.096	0.235
SEVELAMER CARBONATE (O MONTH)	50	45.68	2284			
FERRIC CITRATE (3 MONTH)	50	56.87	2843.5	931.50	0.028	0.310
SEVELAMER CARBONATE (3 MONTH)	50	44.13	2206.5			
FERRIC CITRATE (6 MONTH)	50	64.5	3225	550.00	0.000	0.682
SEVELAMER CARBONATE (6 MONTH)	50	36.5	1825			
FERRIC CITRATE (12 MONTH)	50	66.26	3313	462.00	0.000	0.768
SEVELAMER CARBONATE (12 MONTH)	50	34.74	1737			

INTERPRETATION:

At 0 months there was no significant difference in the iron level between ferric citrate and sevelamer carbonate (i.e. P - 0.096) Suggests Ferric citrate is not inferior to sevelamer carbonate in increasing iron stores in CKD patients, whereas at 3, 6 and 12 months, a significant difference in the iron level between ferric citrate and sevelamer carbonate was found in our study (i.e. P – 0.028, <0.001 and <0.001 respectively). Suggests Ferric citrate is superior to sevelamer carbonate in increasing iron stores in CKD patients after 12 months of respective treatment.

TABLE 9: SERUM FERRITIN IN PATIENTS OVER ONE YEAR IN EACH GROUP

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTHS	268.74	463.32
3 MONTHS	288.976	455.8
6 MONTHS	330.78	390.42
12 MONTHS	430.18	390.88

In the ferric citrate group, mean serum ferritin increased from 268.74 (at 0 months) to 430.18 (at 12 months). Whereas in the sevelamer carbonate group, mean serum ferritin decreased from 463.32 (at 0 months) to 390.88 (at 12 months).

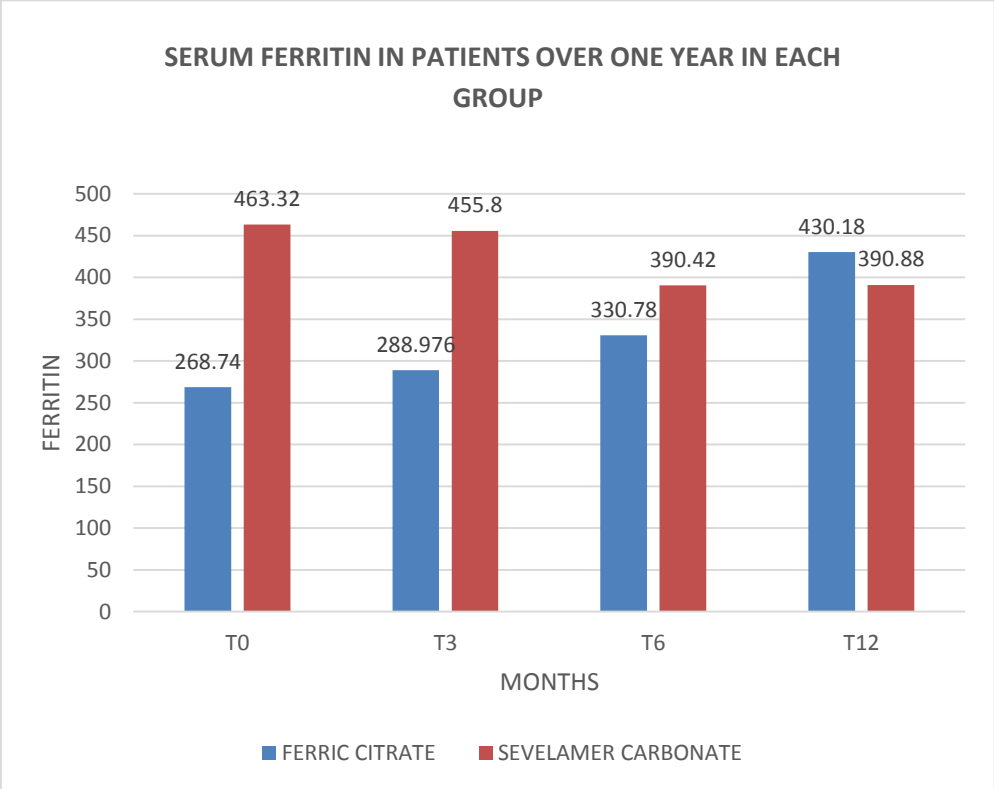


FIGURE 6: SERUM FERRITIN IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 10: RESULTS OF SERUM FERRITIN IN PATIENTS OVER ONE YEAR IN EACH GROUP:

GROUP	N	Mean rank	Sum of ranks	U value	P value	R value
FERRIC CITRATE (O MONTH)	50	43.89	2194.50	919.500	.023	0.322
SEVELAMER CARBONATE (O MONTH)	50	57.11	2855.50			
FERRIC CITRATE (3 MONTH)	50	44.39	2219.50	944.500	.035	0.297
SEVELAMER CARBONATE (3 MONTH)	50	56.61	2830.50			
FERRIC CITRATE (6 MONTH)	50	45.62	2281.00	1006.00	.093	0.237
SEVELAMER CARBONATE (6 MONTH)	50	55.38	2769.00			
FERRIC CITRATE (12 MONTH)	50	47.00	2350.00	1075.00	.228	0.170
SEVELAMER CARBONATE (12 MONTH)	50	54.00	2700.00			

INTERPRETATION: At 0 and 3 months a significant difference in the ferritin level between ferric citrate and sevelamer carbonate was present (P - 0.023 and 0.035 respectively). Serum ferritin in the ferric citrate group was significantly lower than the sevelamer carbonate group at baseline and increased at 3 months. Suggests ferric citrate is superior to sevelamer carbonate in increasing serum ferritin after 3 months of respective therapy. Whereas at 6 and 12 months there was no significant difference in the ferritin level between ferric citrate and sevelamer carbonate (P - 0.093 AND 0.228 respectively). That is there is a significant increase in serum ferritin in the ferric citrate group as compared to the sevelamer group.

TABLE 11: SERUM TIBC IN PATIENTS OVER ONE YEAR IN EACH GROUP:

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTH	300.84	300.30
3 MONTHS	285.42	300.98
6 MONTHS	270.06	298.92
12 MONTHS	253.42	305.6

In ferric citrate group mean serum TIBC decreased from 300.84 (at 0 month) to 253.42 (at 12 month). Whereas in sevelamer carbonate group mean serum TIBC increased from 300.30 (at 0 month) to 305.6 (at 12 month).

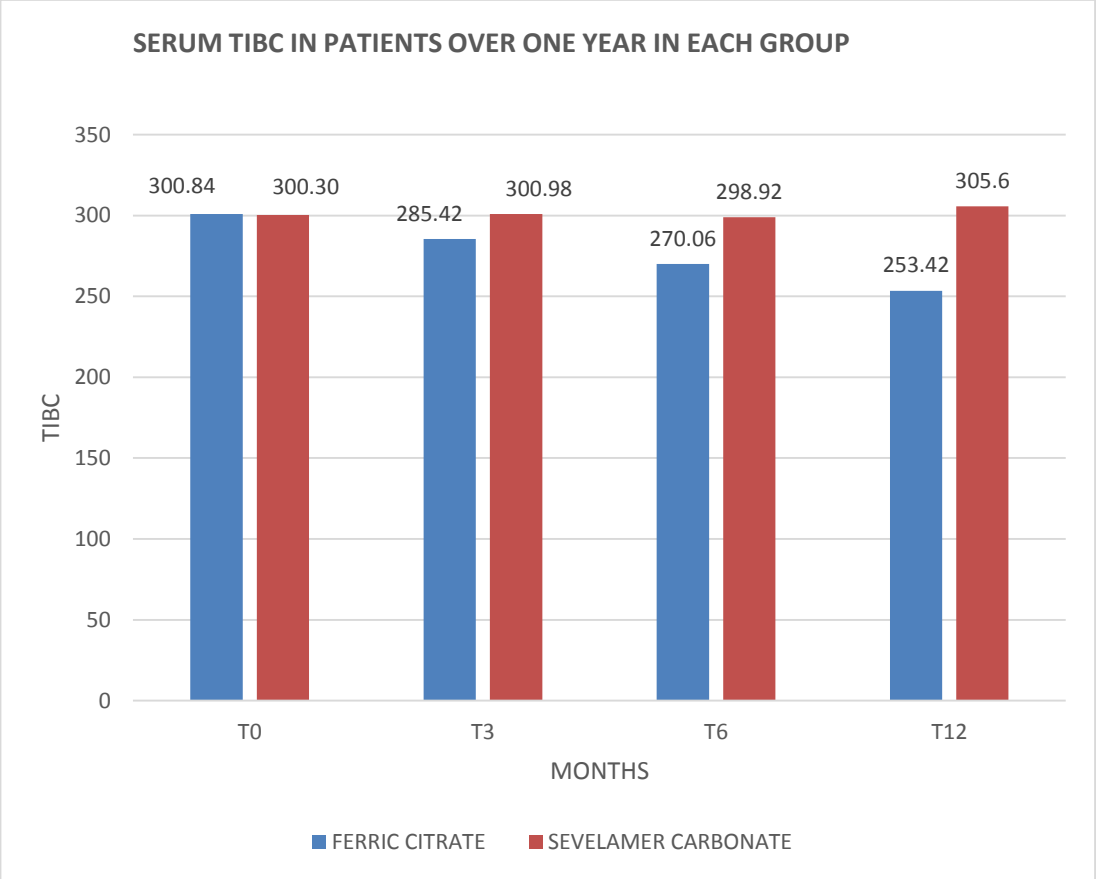


FIGURE 7: SERUM TIBC IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 12: RESULT OF SERUM TIBC IN PATIENTS OVER ONE YEAR IN EACH GROUP

GROUP	N	Mean rank	Sum of ranks	U value	P value	Effect size (R-value)
FERRIC CITRATE (O MONTH)	50	52.23	2611.50	1163.500	.551	0.084
SEVELAMER CARBONATE (O MONTH)	50	48.77	2438.50			
FERRIC CITRATE (3 MONTH)	50	49.45	2472.50	1197.500	.717	0.051
SEVELAMER CARBONATE (3 MONTH)	50	51.55	2577.50			
FERRIC CITRATE (6 MONTH)	50	44.53	2226.50	951.500	.040	0.291
SEVELAMER CARBONATE (6 MONTH)	50	56.47	2823.50			
FERRIC CITRATE (12 MONTH)	50	40.51	2025.50	750.500	.001	0.487
SEVELAMER CARBONATE (12 MONTH)	50	60.49	3024.50			

INTERPRETATION:

At 0 months and 3 months, no significant difference in the TIBC level between ferric citrate and sevelamer carbonate was found. ($p < 0.551$ and < 0.717). Suggests ferric citrate is not inferior to sevelamer carbonate in decreasing TIBC. Whereas at 6- and 12-months a significant difference in the TIBC level between ferric citrate and sevelamer carbonate was found ($p < .040$ and $< .001$). Suggests ferric citrate group is superior to sevelamer carbonate in the reduction of TIBC after 12 months of respective therapy.

TABLE 13: SERUM TRANSFERRIN SATURATION IN PATIENTS OVER ONE YEAR IN EACH GROUP:

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTH	23.126 %	21.154 %
3 MONTHS	26.018 %	20.882 %
6 MONTHS	32.686 %	21.776 %
12 MONTHS	39.81 %	22.184 %

In ferric citrate group mean serum transferrin saturation increased from 23.126 % (at 0 months) to 39.81 % (at 12 months). Whereas in the sevelamer carbonate group mean serum transferrin saturation increased from 21.154 % (at 0 months) to 22.184 % (at 12 months).

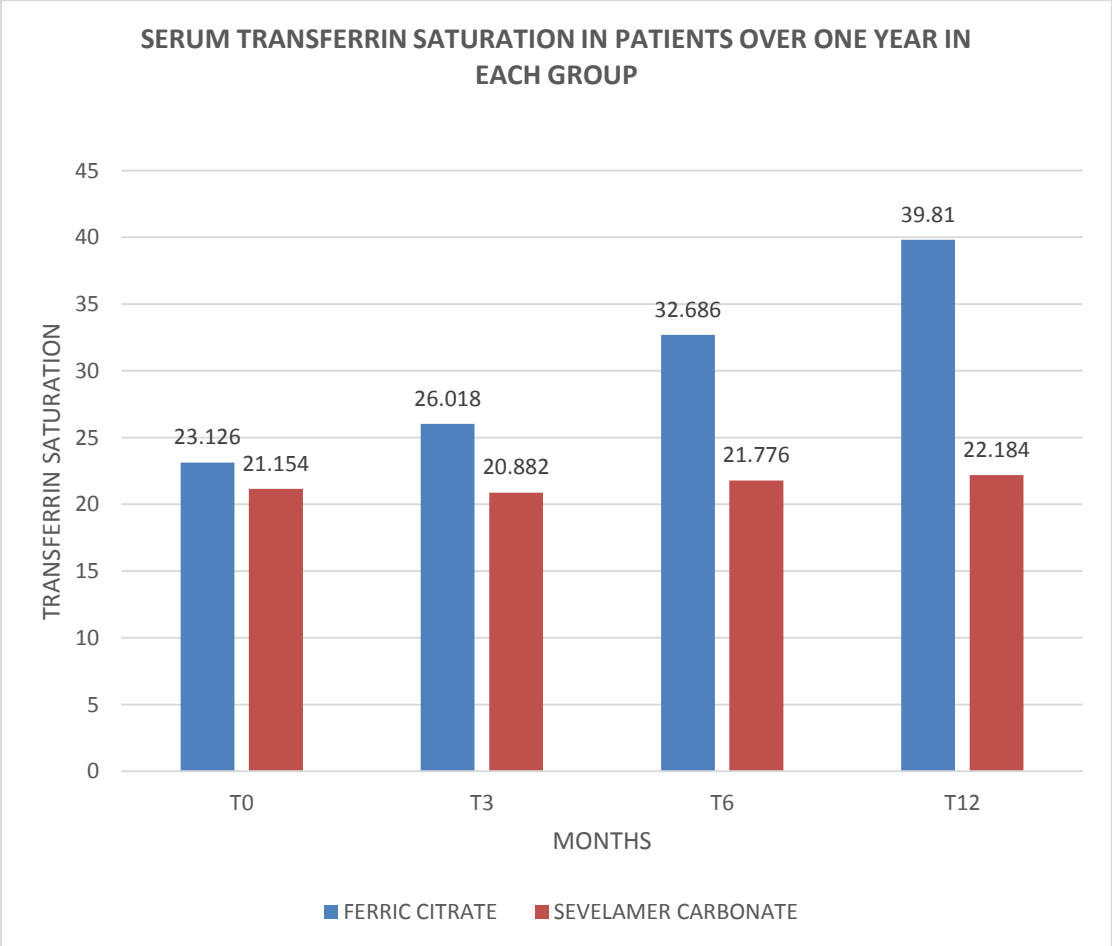


FIGURE 8: SERUM TRANSFERRIN SATURATION IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 14: RESULT OF SERUM TRANSFERRIN SATURATION IN PATIENTS OVER ONE YEAR IN EACH GROUP:

GROUP	N	Mean rank	Sum of ranks	U value	P value	EFFECT SIZE (R-value)
FERRIC CITRATE (O MONTH)	50	53.87	2693.50	1081.50	.245	0.164
SEVELAMER CARBONATE (O MONTH)	50	47.13	2356.50			
FERRIC CITRATE (3 MONTH)	50	57.13	2856.50	918.50	.022	0.323
SEVELAMER CARBONATE (3 MONTH)	50	43.87	2193.50			
FERRIC CITRATE (6 MONTH)	50	63.40	3170.00	605.00	.000	0.629
SEVELAMER CARBONATE (6 MONTH)	50	37.60	1880.00			
FERRIC CITRATE (12 MONTH)	50	67.01	3350.50	424.50	.000	0.804
SEVELAMER CARBONATE (12 MONTH)	50	33.99	1699.50			

INTERPRETATION:

At 0 months no significant difference in the transferrin saturation level between ferric citrate and sevelamer carbonate was found (p- 0.245). Suggests ferric citrate is not inferior to sevelamer carbonate in increasing serum transferrin saturation. Whereas at 3, 6, and 12 months there's a significant difference in the transferrin saturation level between ferric citrate and sevelamer carbonate (p - 0.022, <0.001, <0.001 respectively). Suggests ferric citrate increased serum transferrin saturation was significantly higher than sevelamer carbonate after 12 months of respective therapy. Ferric citrate is superior to sevelamer carbonate in increasing serum transferrin saturation in CKD patients.

TABLE 15: SERUM HAEMOGLOBIN IN PATIENTS OVER ONE YEAR IN EACH GROUP:

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTH	8.75	8.48
3 MONTHS	9.08	8.44
6 MONTHS	9.4	8.36
12 MONTHS	9.89	8.52

In the ferric citrate group, mean serum haemoglobin increased from 8.75 (at 0 months) to 9.89 (at 12 months). Whereas in the sevelamer carbonate group, mean serum haemoglobin increased from 8.48 (at 0 months) to 8.52 (at 12 months).

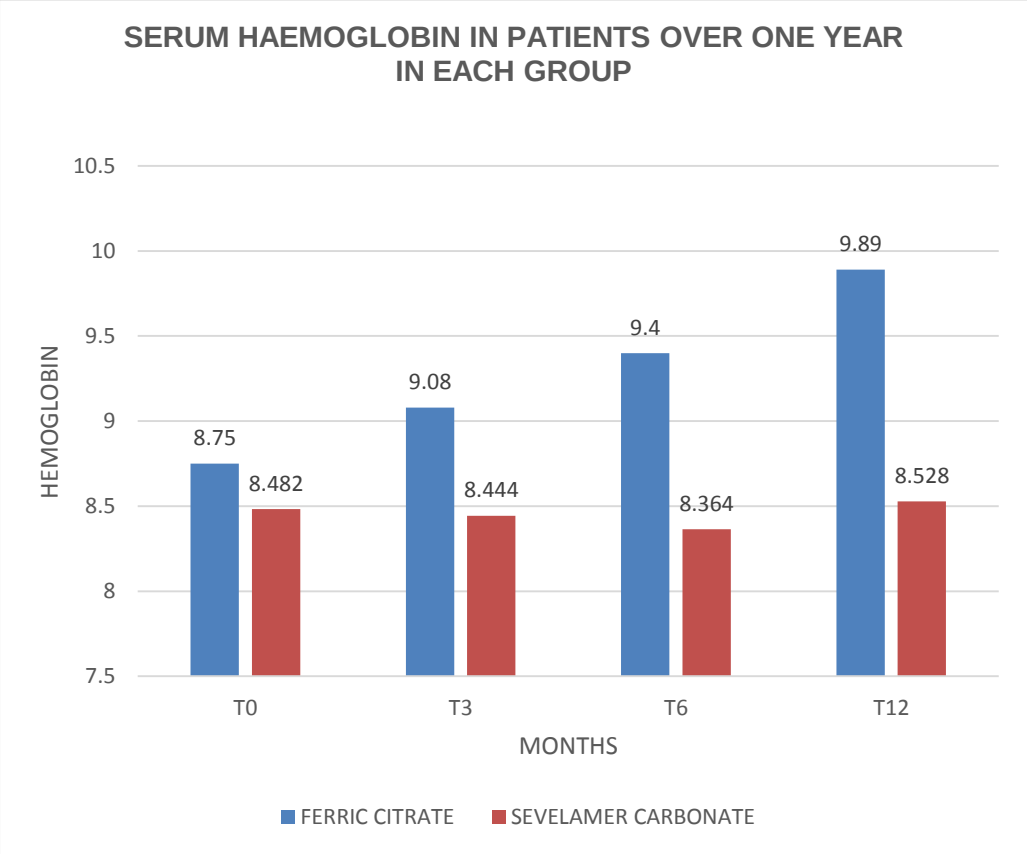


FIGURE 9: SERUM HAEMOGLOBIN IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 16: RESULT OF SERUM HAEMOGLOBIN IN PATIENTS OVER ONE YEAR IN EACH GROUP:

	FERRIC CITRATE		SEVELAMER CARBONATE				
HAEMOGLOBIN	Mean	Standard deviation	Mean	Standard deviation	t (98)	p	Cohen's d
AT 0 MONTH	8.750	1.0706	8.482	1.1714	1.194	.235	0.238831
AT 3 MONTHS	9.080	.94415	8.4440	.95643	3.346	.001	0.669255
AT 6 MONTHS	9.400	.81966	8.3640	.83636	6.256	.000	1.251129
AT 12 MONTHS	9.890	.7232	8.528	.7220	9.425	.000	1.88486

INTERPRETATION:

The difference between the ferric citrate and sevelamer carbonate group was not significant at 0 months (p - 0.235), the mean (SD) change in serum hemoglobin was 8.75 ± 1.07 g/dl in the ferric citrate group versus 8.48 ± 1.17 g/dl in the sevelamer group. Whereas a significant difference was found at 3 months, (p - 0.001), the mean (SD) change in serum hemoglobin was 9.08 ± 0.94 g/dl in the ferric citrate group versus 8.44 ± 0.95 g/dl in the sevelamer group. A significant difference was found at 6 months, (p - <0.001) the mean (SD) change in serum hemoglobin was 9.40 ± 0.81 g/dl in the ferric citrate group versus 8.36 ± 0.83 g/dl in the sevelamer group and difference was significant at 12 months, (p - <0.001) the mean (SD) change in serum hemoglobin was 9.89 ± 0.72 g/dl in the ferric citrate group versus 8.52 ± 0.72 g/dl in the sevelamer group. Suggests Ferric citrate is superior to sevelamer carbonate in increasing serum Hemoglobin after 12 months of respective therapy.

TABLE 17: SERUM PARATHYROID IN PATIENTS OVER ONE YEAR IN EACH GROUP:

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTH	353.88	572.62
3 MONTHS	341.32	740.38
6 MONTHS	345.27	531.14
12 MONTHS	336.98	524.34

In the ferric citrate group mean serum parathyroid decreased from 353.88 (at 0 months) to 336.98 (at 12 months). Whereas in the sevelamer carbonate group mean serum parathyroid decreased from 572.62 (at 0 months) to 524.34 (at 12 months).

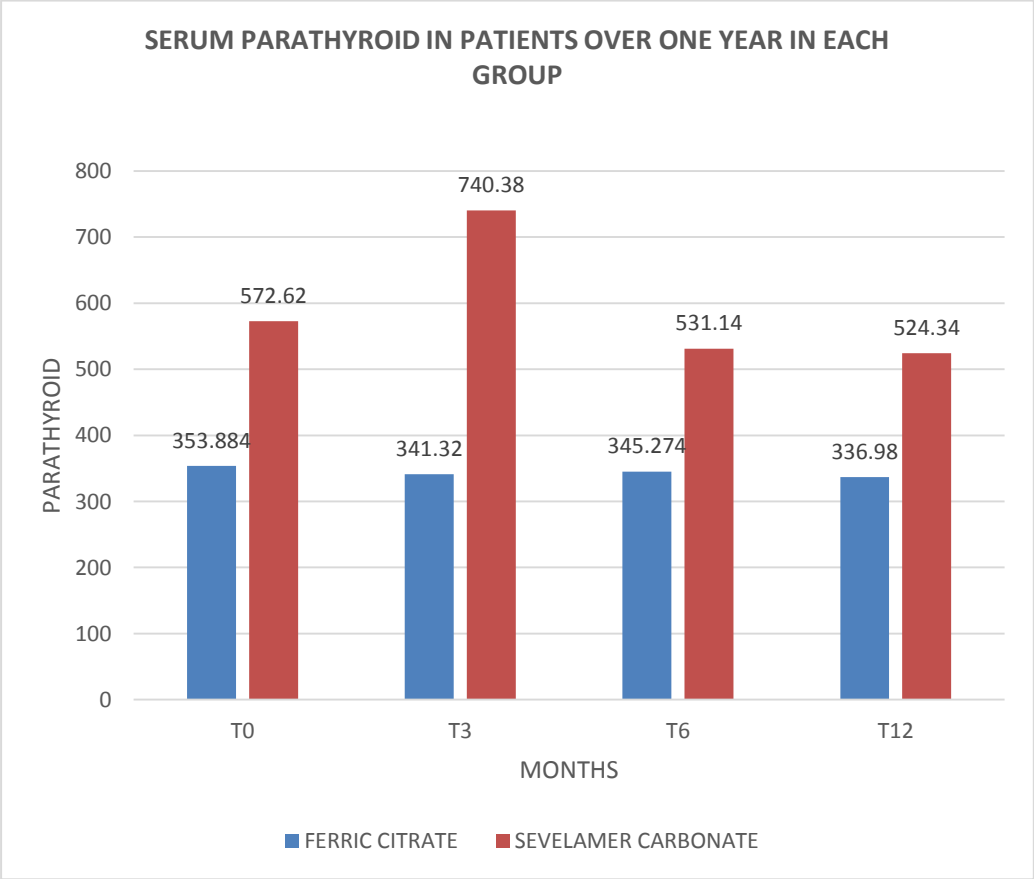


FIGURE 10: SERUM PARATHYROID IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 18: RESULTS OF SERUM PARATHYROID IN PATIENTS OVER ONE YEAR IN EACH GROUP:

GROUP	N	Mean rank	Sum of ranks	U value	P value	Effect size (R-value)
FERRIC CITRATE (O MONTH)	50	42.31	2115.50	840.50	.005	0.399
SEVELAMER CARBONATE (O MONTH)	50	58.69	2934.50			
FERRIC CITRATE (3 MONTH)	50	41.39	2069.50	794.50	.002	0.444
SEVELAMER CARBONATE (3 MONTH)	50	59.61	2980.50			
FERRIC CITRATE (6 MONTH)	50	41.00	2050.00	775.00	.001	0.463
SEVELAMER CARBONATE (6 MONTH)	50	60.00	3000.00			
FERRIC CITRATE (12 MONTH)	50	39.96	1998.00	723.00	.000	0.513
SEVELAMER CARBONATE (12 MONTH)	50	61.04	3052.00			

INTERPRETATION:

At 0, 3, 6, and 12 months a significant difference in the parathyroid level between ferric citrate and sevelamer carbonate was found ($p < 0.005$, $p < 0.002$, $p < 0.001$, $p < 0.001$ respectively). It's suggestive that ferric citrate is superior to sevelamer carbonate in the reduction of parathyroid levels.

TABLE 19: SERUM ALKALINE PHOSPHATE IN PATIENTS OVER ONE YEAR IN EACH GROUP:

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTH	127.36	124.5
3 MONTHS	113.02	123.92
6 MONTHS	100.26	105.14
12 MONTHS	86.62	113.82

In the ferric citrate group, mean serum alkaline phosphate decreased from 127.36 (at 0 months) to 86.62 (at 12 months). Whereas in the sevelamer carbonate group mean serum alkaline phosphate decreased from 124.5 (at 0 months) to 113.82 (at 12 months).

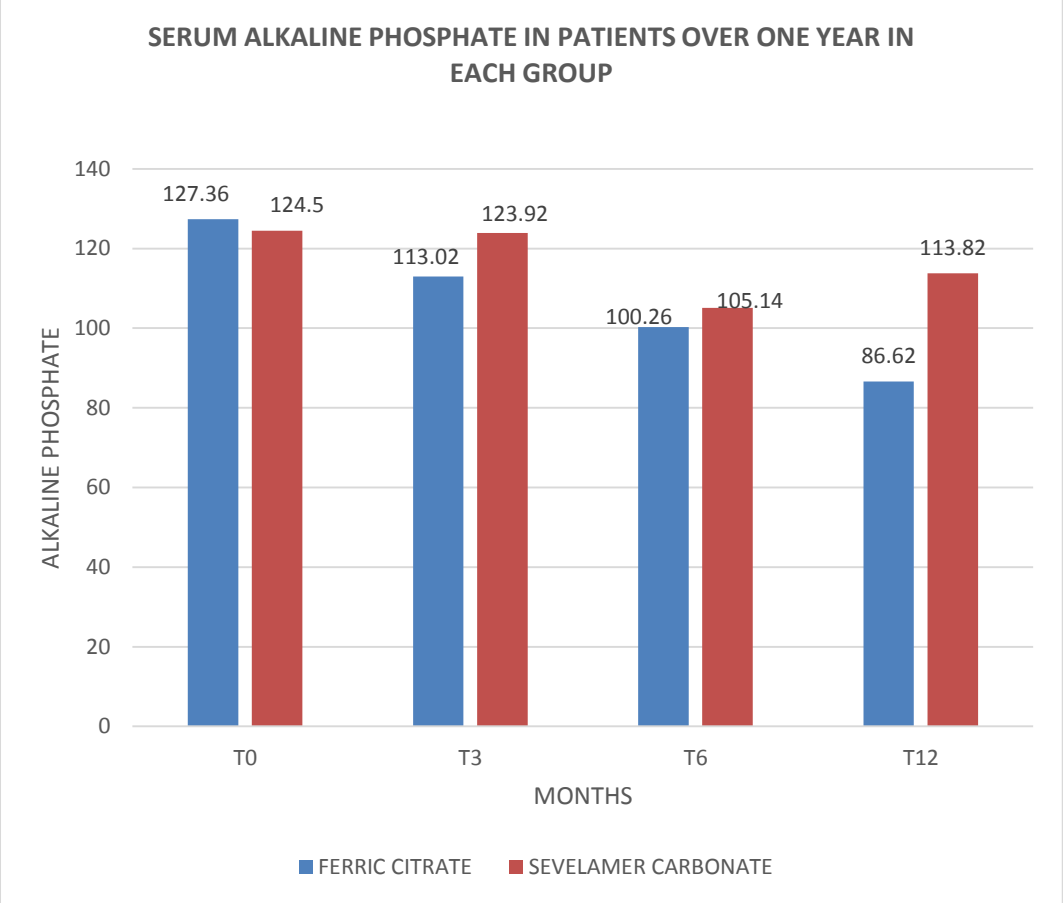


FIGURE 11: SERUM ALKALINE PHOSPHATE IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 20: RESULT OF SERUM ALKALINE PHOSPHATE IN PATIENTS OVER ONE YEAR IN EACH GROUP:

GROUP	N	Mean rank	Sum of ranks	U value	P value	Effect size (R-value)
FERRIC CITRATE (O MONTH)	50	53.73	2686.50	1088.500	.265	0.157
SEVELAMER CARBONATE (O MONTH)	50	47.27	2363.50			
FERRIC CITRATE (3 MONTH)	50	49.80	2490.00	1215.000	.809	0.034
SEVELAMER CARBONATE (3 MONTH)	50	51.20	2560.00			
FERRIC CITRATE (6 MONTH)	50	49.14	2457.00	1182.000	.639	0.066
SEVELAMER CARBONATE (6 MONTH)	50	51.86	2593.00			
FERRIC CITRATE (12 MONTH)	50	44.58	2229.00	954.000	.041	0.288
SEVELAMER CARBONATE (12 MONTH)	50	56.42	2821.00			

INTERPRETATION:

At 0, 3, and 6 months there's no significant difference in the alkaline phosphate level between ferric citrate and sevelamer carbonate (p <0.265, p <0.809, p <0.639 respectively), ferric citrate is not inferior in decreasing alkaline phosphate after 6 months of respective therapy. At 12 months there's a significant difference in the alkaline phosphate level between ferric citrate and sevelamer carbonate (p - <0.041). Suggests ferric citrate is superior in decreasing alkaline phosphate after 12 months of respective therapy.

TABLE 21: SERUM PHOSPHORUS IN PATIENTS OVER ONE YEAR IN EACH GROUP:

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTH	5.838	7.202
3 MONTHS	5.0088	5.2164
6 MONTHS	4.2218	4.4396
12 MONTHS	3.611	3.6264

In the ferric citrate group mean serum phosphorus decreased from 5.838 (at 0 months) to 3.611 (at 12 months). Whereas in the sevelamer carbonate group mean serum phosphorus decreased from 7.202 (at 0 months) to 3.6264 (at 12 months).

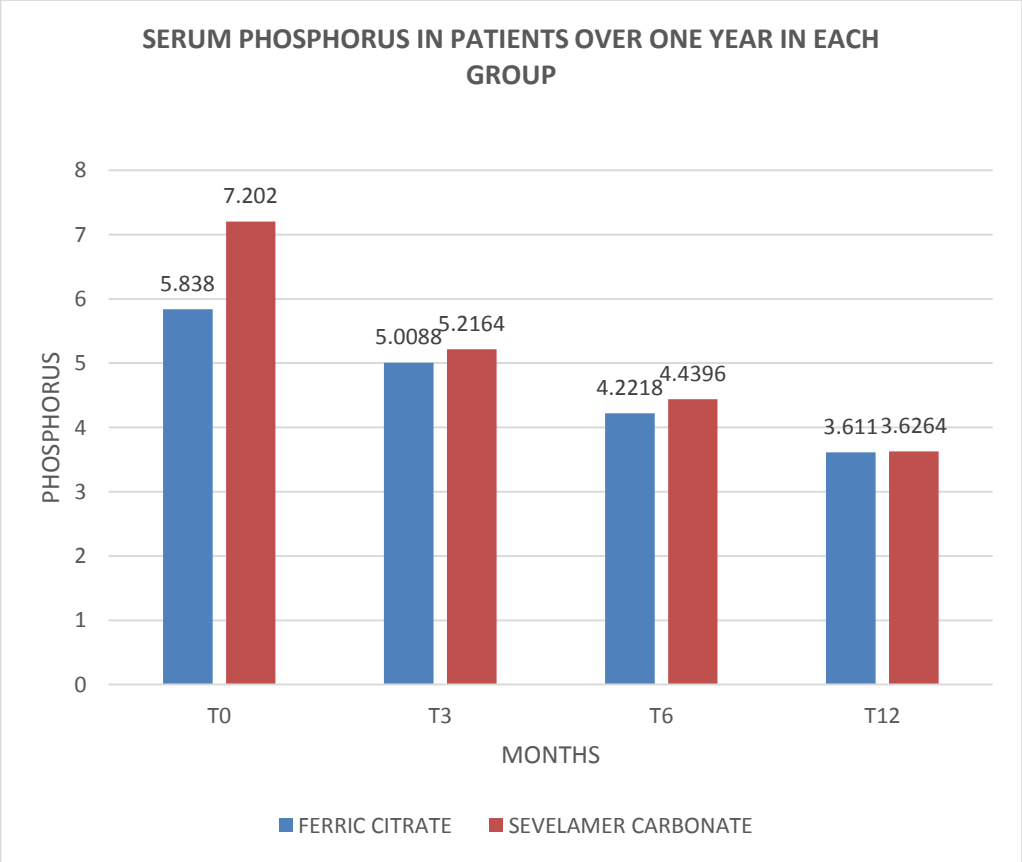


FIGURE 12: SERUM PHOSPHORUS IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 22: RESULT OF SERUM PHOSPHORUS IN PATIENTS OVER ONE YEAR IN EACH GROUP:

GROUP	N	Mean rank	Sum of ranks	U value	P value	Effect size (R-value)
FERRIC CITRATE (O MONTH)	50	46.27	2313.50	1038.500	.144	0.206
SEVELAMER CARBONATE (O MONTH)	50	54.73	2736.50			
FERRIC CITRATE (3 MONTH)	50	44.72	2236.00	961.000	.046	0.282
SEVELAMER CARBONATE (3 MONTH)	50	56.28	2814.00			
FERRIC CITRATE (6 MONTH)	50	42.66	2133.00	858.000	.007	0.382
SEVELAMER CARBONATE (6 MONTH)	50	58.34	2917.00			
FERRIC CITRATE (12 MONTH)	50	48.93	2446.50	1171.500	.587	0.076
SEVELAMER CARBONATE (12 MONTH)	50	52.07	2603.50			

INTERPRETATION: At 0 months, there is no significant difference in the phosphorus level between FC and SC (p = 0.144). Ferric citrate is not inferior to sevelamer carbonate in reducing serum phosphorus. Whereas at 3- and 6- months, a significant difference in the phosphorus level between ferric citrate and sevelamer carbonate groups (p - 0.046, 0.007) suggests that ferric citrate was superior to sevelamer in decreasing serum phosphorus between 3 and 6 months. But at 12 months again, there is no significant difference in the phosphorus level between ferric citrate and sevelamer carbonate. Ferric citrate is not inferior to sevelamer carbonate in reducing serum phosphorus after 12 months of respective therapy.

TABLE 23: SERUM CALCIUM IN PATIENTS OVER ONE YEAR IN EACH GROUP:

MONTHS	FERRIC CITRATE	SEVELAMER CARBONATE
O MONTH	8.41	8.24
3 MONTHS	8.69	8.3
6 MONTHS	8.89	8.35
12 MONTHS	9.09	8.45

In the ferric citrate group mean serum calcium increased from 8.41 (at 0 months) to 9.09 (at 12 months). Whereas in the sevelamer carbonate group, mean serum calcium increased from 8.24 (at 0 months) to 8.45 (at 12 months).

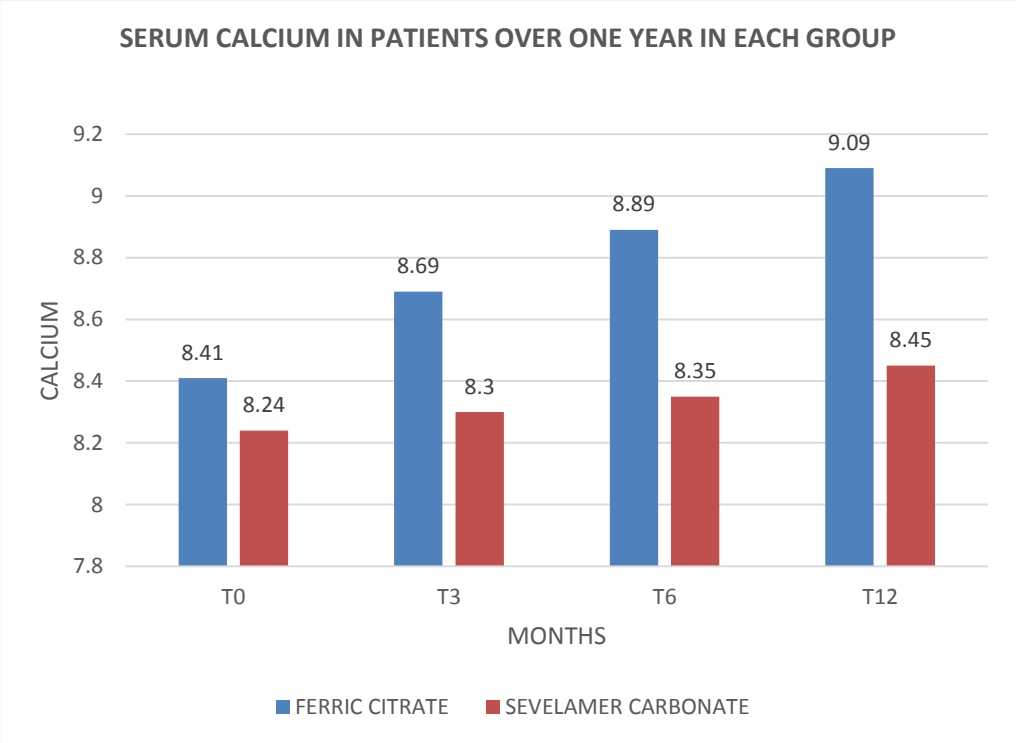


FIGURE 13: SERUM CALCIUM IN PATIENTS OVER ONE YEAR IN EACH GROUP

TABLE 24: RESULT OF SERUM CALCIUM IN PATIENTS OVER ONE YEAR IN EACH GROUP:

GROUP	N	Mean rank	Sum of ranks	U value	P value	Effect size (R-value)
FERRIC CITRATE (O MONTH)	50	53.81	2690.50	1084.500	.253	0.161
SEVELAMER CARBONATE (O MONTH)	50	47.19	2359.50			
FERRIC CITRATE (3 MONTH)	50	57.02	2851.00	924.000	.024	0.318
SEVELAMER CARBONATE (3 MONTH)	50	43.98	2199.00			
FERRIC CITRATE (6 MONTH)	50	61.64	3082.00	693.000	.000	0.544
SEVELAMER CARBONATE (6 MONTH)	50	39.36	1968.00			
FERRIC CITRATE (12 MONTH)	50	65.64	3282.00	493.000	.000	0.739
SEVELAMER CARBONATE (12 MONTH)	50	35.36	1768.00			

INTERPRETATION:

At 0 months, there was no significant difference in the calcium level between ferric citrate and sevelamer carbonate (p <.253). Ferric citrate is not inferior to sevelamer in decreasing calcium levels at 0 months. At 3, 6, and 12 months, a significant difference in the calcium level between ferric citrate and sevelamer carbonate was found (p <.024, p <0.001, and p <0.001, respectively). Ferric citrate is inferior to sevelamer carbonate in decreasing serum calcium levels.

DISCUSSION

Chronic kidney disease is acknowledged as a serious public health issue. An estimated 13.4% of people worldwide are expected to have CKD. Although over 5.9 million people worldwide rely on dialysis or functional kidney transplantation to survive, the vast majority of CKD patients do not. Iron deficiency anemia and hyperphosphatemia are the most prevalent abnormalities in patients with CKD and are both independent risk factors for cardiovascular disease.

The study was conducted in the Department of Medicine and other Allied Specialties of Medicine in DMC & Hospital Ludhiana. A total of 100 patients were enrolled and were treated with either ferric citrate or sevelamer carbonate over 1 year in outdoor departments of the hospital. Patients were categorized in CKD stages according to KDIGO classification. Clinical and laboratory data of all 100 patients was pooled together after their informed consent and was analyzed.

- **GENDER DISTRIBUTION:** In our study, out of 100 patients,50 patients were in ferric citrate group - 26 (52%) patients were males and 24 (48%) were females with male to female ratio - 1.1:1 and 50 patients were in sevelamer group - 28 (56%) patients were males and 22 (44%) were females in sevelamer carbonate group with male to female ratio - 1.3:1. Similar ratio were found in Geoffrey a. Block et al [126] male to female ratio was 1.01:1, Peter a. Mccullough et al [127] male to female ratio was 1.1 :1, Ketteler, Markus & Rix et al [122] male to female ratio was 2:1. Whereas in Glenn m. Chertow et al [125] male to female ratio was 0.5:1, here females were more than males.

- **CATEGORY DISTRIBUTION:** Most of the patients in the FC group were from CKD CATEGORY IV (76%) followed by CKD III (16%) and CKD V (8%). Most of the patients in the SC group were from CKD CATEGORY IV (78%) followed by CKD V (12%) and CKD III

(10%). In previous studies like - Glenn M. Chertow et al [125] most common category was CKD IV (46%) followed by CKD III (41%) and CKD V (13%). In Geoffrey A. Block et al [126] CKD V (41%) followed by CKD IV (33%) and CKD III (24%). Peter a. Mccullough et al [127] CKD IV (45%) followed by CKD III (40%) and CKD V (15%), whereas in Ketteler, Markus & Rix et al [122] CKD V (65%) followed by CKD IV (35%).

TABLE 25 : DIFFERENT STUDIES WITH CKD CATEGORY:

STUDY	CKD III	CKD IV	CKD V
Ferric citrate	16%	76%	8%
Sevelamer carbonate	10%	78%	12%
Glenn M. Chertow et al	41%	46%	13%
Geoffrey A. Block et al	24%	33%	41%
Peter a. Mccullough et al	40%	45%	15%
Ketteler, Markus & Rix et al	--	35%	65%

- **AGE DISTRIBUTION:** Most of the FC group patients were in the age of >40 years (82%) and most of the SC group patients were also in the same age group of >40 years (88%). A similar age group was present in past studies - Geoffrey A. Block et al [126], Peter A. Mccullough et al [127], Glenn M. Chertow et al [125], and Ketteler, Markus & Rix et al [122] mean age was >50 years of the patient enrolled in the respective studies.

- **SERUM IRON:** In the FC group mean serum iron increased from 66.87 (at 0 months) to 105.95 (at 12 months). Whereas in the SC group mean serum iron increased from 58.99 (at 0 months) to 61.85 (at 12 months).

  At 0 months there was no statistically significant difference in the iron level between the FC and SC group (i.e. P - 0.096) Suggestive of Ferric citrate is not inferior to sevelamer carbonate in increasing iron stores in CKD patients, whereas at 3, 6, and 12 months, a

statistically significant difference in the iron level between ferric citrate and sevelamer carbonate was found in our study (i.e. P – 0.028, <0.001 and <0.001 respectively). Suggests Ferric citrate is superior to sevelamer carbonate in increasing iron stores in CKD patients after 12 months of respective treatment.

- **SERUM FERRITIN:** In the FC group mean serum ferritin increased from 268.74 pmol/L (at 0 months) to 430.18 pmol/L (at 12 months). Whereas in the SC group mean serum ferritin decreased from 463.32 pmol/L (at 0 months) to 390.88 pmol/L (at 12 months).

  At 0 and 3 months a statistically significant difference in the ferritin level between ferric citrate and sevelamer carbonate was present (P - 0.023 and 0.035 respectively). Serum ferritin in the ferric citrate group was significantly lower than the sevelamer carbonate group at baseline and increased at 3 months. Suggests ferric citrate is superior to sevelamer carbonate in increasing serum ferritin after 3 months of respective therapy.

  Whereas at 6 and 12 months there was no statistically significant difference in the ferritin level between ferric citrate and sevelamer carbonate (P - 0.093 AND 0.228 respectively). That is there is a significant increase in serum ferritin in the ferric citrate group as compared to the sevelamer group.

  A similar trend of increase in serum ferritin with the use of ferric citrate has been seen in past studies, Geoffrey A. Block et al [126] over 9 months of study, The mean (SD) change seen in serum ferritin was 202 ± 173 pmol/L in the ferric citrate group versus 170 ± 169 pmol/L in the placebo group. Glenn m. Chertow et al [125] over 12 weeks of study the mean (SD) change seen in serum ferritin was 220 ± 155 pmol/L in the ferric citrate group versus 208 ± 155 pmol/L in the placebo group and Peter a. Mccullough et al [127] over 16 weeks. The mean (SD) change seen in serum ferritin was 201.6 ± 172.3 pmol/L in the ferric citrate group versus –27.4 ± 66.5 pmol/L in the placebo group.

- **SERUM TIBC:** In the FC group mean serum TIBC decreased from 300.84 (at 0 months) to 253.42 (at 12 months). Whereas in the SC group, serum TIBC increased from 300.30 (at 0 months) to 305.6 (at 12 months).

  At 0 months and 3 months, no statistically significant difference in the TIBC level between ferric citrate and sevelamer carbonate was found. (p <0.551 and <0.717). Suggests ferric citrate is not inferior to sevelamer carbonate in decreasing TIBC. Whereas at 6- and 12-months a statistically significant difference in the TIBC level between ferric citrate and sevelamer carbonate was found (p <.040 and <0.001). Suggests ferric citrate group is superior to sevelamer carbonate in the reduction of TIBC after 12 months of respective therapy.

- **SERUM TRANSFERRIN SATURATION:** In the FC group mean serum transferrin saturation increased from 23.126 % (at 0 months) to 39.81 % (at 12 months). Whereas in the SC group mean serum transferrin saturation increased from 21.154 % (at 0 months) to 22.184 % (at 12 months).

  At 0 months no statistically significant difference in the transferrin saturation level between ferric citrate and sevelamer carbonate was found (p- 0.245). Suggests ferric citrate is not inferior to sevelamer carbonate in increasing serum transferrin saturation. Whereas at 3, 6, and 12 months there's a statistically significant difference in the transferrin saturation level between ferric citrate and sevelamer carbonate (p - 0.022, <0.001, <0.001 respectively). Suggests ferric citrate increased serum transferrin saturation was significantly higher than sevelamer carbonate after 12 months of respective therapy.

A similar trend of increase in serum transferrin saturation with treatment with ferric citrate has been seen in Geoffrey A. Block et al [126] over 9 months of study, the mean (SD) change seen in serum transferrin saturation was 25 ± 9% in the FC group versus 23 ± 9 % in the placebo group. Glenn m. Chertow et al [125] over 12 weeks of study

the mean (SD) change seen in serum transferrin saturation was 20.9 ± 6.8% in the FC group versus 20.3 ± 7.4% in the placebo group. And to Peter A. Mccullough et al [127] over 16 weeks the mean (SD) change seen in serum transferrin saturation was 13.7 ± 10.9 % in the FC group versus 7.7 ± 1.3 % in the placebo group.

- **SERUM HEMOGLOBIN:** In the FC group mean serum haemoglobin increased from 8.75 g/dl (at 0 months) to 9.89 g/dl (at 12 months). Whereas in the SC group mean serum haemoglobin increased from 8.48 g/dl (at 0 months) to 8.52 g/dl (at 12 month).

  Difference between ferric citrate and sevelamer carbonate group was not statistically significant at 0 months (p - 0.235), the mean (SD) change in serum hemoglobin was 8.75 ± 1.07 g/dl in the ferric citrate group versus 8.48 ± 1.17 g/dl in the sevelamer group. Whereas a statistically significant difference was found at 3 months, (p - 0.001), the mean (SD) change in serum hemoglobin was 9.08 ± 0.94 g/dl in the ferric citrate group versus 8.44 ± 0.95 g/dl in the sevelamer group. A statistically significant difference was found at 6 months, (p - <0.001) the mean (SD) change in serum hemoglobin was 9.40 ± 0.81 g/dl in the ferric citrate group versus 8.36 ± 0.83 g/dl in the sevelamer group and difference was statistically significant at 12 months, (p - <0.001) the mean (SD) change in serum hemoglobin was 9.89 ± 0.72 g/dl in the ferric citrate group versus 8.52 ± 0.72 g/dl in the sevelamer group. Suggests Ferric citrate is superior to sevelamer carbonate in increasing serum Hemoglobin after 12 months of respective therapy.

  Similar results were seen with the increase in serum Hemoglobin with the use of ferric citrate have been seen in Geoffrey a. Block et al [126] over 9 months of study the mean (SD) change seen in serum hemoglobin was 11.3 ± 1.6 g/dl in the FC group versus 11 ± 1.6 g/dl in the placebo group, Glenn m. Chertow et al [125] over 12 weeks of study with the mean (SD) change seen in serum hemoglobin was 10.48 ± 0.76 g/dl in the FC group versus 10.47 ± 0.90 g/dl in the placebo group and Peter a. Mccullough et al [127] over 16 weeks with the mean (SD)

change seen in serum hemoglobin was 7.3 ± 4.1 g/dl in the FC group versus 6.4 ± 2.1 g/dl in the placebo group.

- **SERUM PHOSPHORUS:** In the FC group mean serum phosphorus decreased from 5.83 mg/dl (at 0 months) to 3.61 mg/dl (at 12 months). Whereas in the SC group mean serum phosphorus decreased from 7.20 mg/dl (at 0 months) to 3.62 mg/dl (at 12 months).

  At 0 months, there is no statistically significant difference in the phosphorus level between ferric citrate and sevelamer carbonate (p = 0.144). Ferric citrate is not inferior to sevelamer carbonate in reducing serum phosphorus. Whereas at 3 and 6 months, a statistically significant difference in the phosphorus level between ferric citrate and sevelamer carbonate (p - 0.046, 0.007) suggests that ferric citrate was superior to sevelamer in decreasing serum phosphorus between 3 and 6 months. But at 12 months again, there is no statistically significant difference in the phosphorus level between ferric citrate and sevelamer carbonate. Ferric citrate is not inferior to sevelamer carbonate in reducing serum phosphorus after 12 months of respective therapy.

  Similar results of phosphorus reduction by ferric citrate were also seen in Glenn M. Chertow et al. [125]. The mean (SD) change seen in serum phosphorus was 4.34 ± 0.81 mg/dl in the FC group versus 4.33 ± 0.70 mg/dl in the placebo group. Serum phosphate decrease was also seen in Geoffrey A. Block et al. [126]. The mean (SD) change seen in serum phosphorus was 4.5 ± 0.9 mg/dl in the FC group versus 4.4 ± 0.7 mg/dl in the placebo group. Serum phosphorus decrease was also seen in Peter A. Mccullough et al. [127]. The mean (SD) change seen in serum phosphorus was 4.68 ± 0.9 mg/dl in the FC group versus 3.96 ± 0.8 mg/dl in the placebo group.

  Phosphorus reduction by sevelamer was seen in Ketteler, Markus & Rix et al. [122]. The mean (SD) change in serum phosphorus was 4.8 ± 1.0 mg/dl from a baseline of 6.2 ± 0.8 mg/dl after 8 weeks of treatment with sevelamer carbonate. Vincenzo Savica et al. [123]. The mean (SD) change in serum phosphorus was 4.6 ± 0.9 mg/dl from the baseline of 6.2 ± 0.8 mg/dl after 8 weeks of treatment with sevelamer carbonate,

as reported by Chen, Nan, and Wu et al. [124]. The mean (SD) change in serum phosphorus was 5.82 ± 1.55 mg/dl from the baseline of 7.95 ± 1.94 mg/dl after 8 weeks of treatment with sevelamer carbonate.

- **SERUM PARATHYROID:** In the FC group mean serum parathyroid decreased from 353.88 pg/ml (at 0 months) to 336.98 pg/ml (at 12 months). Whereas in the SC group mean serum parathyroid decreased from 572.62 pg/ml (at 0 months) to 524.34 pg/ml (at 12 months).

  At 0,3,6 and 12 months a statistically significant difference in the parathyroid level between ferric citrate and sevelamer carbonate was found ($p < 0.005$, $p < 0.002$, $p < 0.001$, $p < 0.001$ respectively). It's suggestive that ferric citrate is superior to sevelamer carbonate in the reduction of parathyroid levels.

  Similar results of serum parathyroid were seen in Geoffrey A. Block et al [126] after 9 months of study the mean (SD) change in serum parathyroid was 207 ± 152 pg/ml in the ferric citrate group versus 213 ± 178 pg/ml in the placebo group.

- **SERUM CALCIUM:** In the FC group mean serum calcium increased from 8.41 mg/dl (at 0 months) to 9.09 mg/dl (at 12 months). In the SC group, serum calcium increased from 8.24 mg/dl (at 0 months) to 8.45 mg/dl (at 12 months).

  At 0 months, there was no statistically significant difference in the calcium level between ferric citrate and sevelamer carbonate ($p < 0.253$). Ferric citrate is not inferior to sevelamer in decreasing calcium levels at 0 months.

  At 3, 6, and 12 months, a statistically significant difference in the calcium level between ferric citrate and sevelamer carbonate was found ($p < 0.024$, $p < 0.001$, $p < 0.001$ respectively). Ferric citrate is inferior to sevelamer carbonate in decreasing serum calcium levels.

  Similar results were seen in a past study - Ketteler, Markus & Rix et al [122] the mean (SD) change in serum calcium was 8.8 ± 0.8 mg/dl from a baseline of 8.5 ± 0.9 mg/dl after 8 wk of treatment with sevelamer carbonate.

- **SERUM ALP:** In the FC group mean serum alkaline phosphate decreased from 127.36 u/l (at 0 months) to 86.62 u/l (at 12 months). In the SC group, the mean serum alkaline phosphate decreased from 124.5 u/l (at 0 months) to 113.82 u/l (at 12 months).

  At 0, 3, and 6 months there's no statistically significant difference in the alkaline phosphate level between ferric citrate and sevelamer carbonate ($p < 0.265$, $p < 0.809$, $p < 0.639$ respectively), ferric citrate is not inferior in decreasing alkaline phosphate after 6 months of respective therapy. At 12 months there's a statistically significant difference in the alkaline phosphate level between ferric citrate and sevelamer carbonate (p - <0.041). Suggests ferric citrate is superior in decreasing alkaline phosphate after 12 months of respective therapy.

  Thus, our study showed that gender distribution in patients with CKD has more males than females in both groups. With the most common CKD category being CKD IV. With most patient being in 5^{th} decade of their life. Compared to sevelamer carbonate in patients with CKD, Ferric citrate has a better profile for managing anemia secondary to chronic illness and reduces the use of erythropoietin-stimulating agents. Ferric citrate has shown a better response in increasing serum iron levels, serum transferrin saturation, serum ferritin, and serum Hemoglobin in patients with chronic kidney disease if compared to sevelamer carbonate with therapy given over 12 months. Ferric citrate has shown a better response in decreasing serum parathyroid levels, serum total iron binding capacity (TIBC), and serum alkaline phosphate in patients with CKD if compared to sevelamer carbonate with therapy given over 12 months. Sevelamer carbonate has shown a better response in decreasing serum calcium levels in patients with CKD than ferric citrate with treatment over 12 months. Ferric citrate is not inferior to sevelamer in lowering serum phosphorus levels in patients with CKD when therapy is given over 12 months. Ferric citrate can be considered over sevelamer carbonate for its better response over

anemia profile and non-inferior phosphorus reduction when compared to other phosphate binders in patients with CKD-ND III TO V.

SUMMARY AND CONCLUSION

SUMMARY

- The study was done in the Department of Medicine and other Allied Specialties of Medicine in DMC & Hospital Ludhiana.
- A total of 100 patients were enrolled and were treated with either ferric citrate or sevelamer carbonate over 1 year in outdoor departments of the hospital.
- Patients were categorized in CKD stages according to KDIGO classification.
- Clinical and laboratory data of all 100 patients was pooled together after their informed consent and was analyzed.
- 100 patients were enrolled,50 patients were in the ferric citrate group - 26 (52%) - were males and 24 (48%) - were females with M: F - 1.1:1, and 50 patients were in the sevelamer group - 28 (56%) - males and 22 (44%) - females in sevelamer carbonate group with M: F - 1.3:1.
- Most patients in both groups were in the age group of >40 years, 82% -ferric citrate and 88% - sevelamer carbonate.
- Most of the patients in the ferric citrate group were from CKD IV (76%) < CKD III (16%) < CKD V (8%) and in the sevelamer carbonate group were from CKD IV (78%) < CKD V (12%) < CKD III (10%).
- Mean serum iron in the ferric citrate group increased from 66.87 (at 0 months) to 105.95 (at 12 months) and in the sevelamer carbonate group increased from 58.99 (at 0 months) to 61.85 (at 12 months).
- Ferric citrate is superior to sevelamer carbonate in increasing iron stores in CKD patients after 12 months of respective treatment.
- Mean serum ferritin in the ferric citrate group increased from 268.74 pmol/L (at 0 months) to 430.18 pmol/L (at 12 months) and in the sevelamer carbonate group decreased from 463.32 pmol/L (at 0 months) to 390.88 pmol/L (at 12 months).

- Ferric citrate is superior to sevelamer carbonate in increasing serum ferritin after 3 months of respective therapy. There is a significant increase in serum ferritin in ferric citrate as compared to sevelamer carbonate.
- Mean serum TIBC in the ferric citrate group decreased from 300.84 (at 0 month) to 253.42 (at 12 months) and in the sevelamer carbonate group increased from 300.30 (at 0 months) to 305.6 (at 12 months).
- Ferric citrate group is superior to sevelamer carbonate in reduction of TIBC after 12 months of respective therapy.
- Mean serum transferrin saturation in the ferric citrate group increased from 23.126 % (at 0 month) to 39.81 % (at 12 months) and in the sevelamer carbonate group increased from 21.154 % (at 0 months) to 22.184 % (at 12 months).
- Ferric citrate is superior to sevelamer carbonate in increasing serum transferrin saturation after 12 months of respective therapy.
- Mean serum hemoglobin in the ferric citrate group increased from 8.75 g/dl (at 0 months) to 9.89 g/dl (at 12 months) and in the sevelamer carbonate group increased from 8.48 g/dl (at 0 months) to 8.52 g/dl (at 12 months). The mean (SD) change in serum hemoglobin was 9.89 ± 0.72 g/dl in the ferric citrate group versus 8.52 ± 0.72 g/dl in the sevelamer group.
- Ferric citrate is superior to sevelamer carbonate in increasing serum Hemoglobin after 12 months of respective therapy.
- Mean serum phosphorus in the ferric citrate group decreased from 5.83 mg/dl (at 0 months) to 3.61 mg/dl (at 12 months) and in the sevelamer carbonate group decreased from 7.20 mg/dl (at 0 months) to 3.62 mg/dl (at 12 months).
- Ferric citrate is not inferior to sevelamer carbonate in reducing serum phosphorus after 12 months of respective therapy.
- Mean serum parathyroid in the ferric citrate group decreased from 353.88 pg/ml (at 0 months) to 336.98 pg/ml (at 12 months)

and in the sevelamer carbonate group decreased from 572.62 pg/ml (at 0 months) to 524.34 pg/ml (at 12 months).

- Ferric citrate is superior to sevelamer carbonate in the reduction of parathyroid levels
- Mean serum calcium in the ferric citrate group increased from 8.41 mg/dl (at 0 months) to 9.09 mg/dl (at 12 months) and in the sevelamer carbonate group increased from 8.24 mg/dl (at 0 months) to 8.45 mg/dl (at 12 months).
- Ferric citrate is inferior to sevelamer carbonate in decreasing serum calcium levels.
- Mean serum alkaline phosphate in the ferric citrate group decreased from 127.36 u/l (at 0 months) to 86.62 u/l (at 12 months) and in the sevelamer carbonate group decreased from 124.5 u/l (at 0 months) to 113.82 u/l (at 12 months).
- Ferric citrate is superior in decreasing alkaline phosphate after 12 months of respective therapy.

CONCLUSION

Chronic kidney disease continues to have high mortality and morbidity. Anemia and hyperphosphatemia were key etiology behind multiple complications associated with CKD. Sevelamer carbonate has been aggressively used as a phosphate binder in CKD-ND whereas it has minimal impact on anemia secondary to CKD. In contrast, ferric citrate has a better response on the anemia profile of patients with chronic kidney disease and also non-inferior action on hyperphosphatemia. Hence ferric citrate can be used in CKD ND with hyperphosphatemia and anemia over sevelamer carbonate.

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SR.NO	MRD NO	NAME	AGE	SEX	CITY	CHIEF COMPLAINS	COMORBIDITIES (IF ANY)	DIAGNOSIS	CATEGORY	GFR	ALBUMIN	BP	HR	SPO2	RR	IRON AT 0 MONTH	IRON AT 3 MONTH
1	1460407	RA	30	MALE	LUDHIANA	HIGH BLOOD PRESSURE	HTN	HTN CKD	CKD V	15	2+	140/80	94	98	16	12.5	30
2	1440408	S	19	FEMALE	LUDHIANA	SOB	NONE	CKD	CKD IV	18	1+	120/70	86	94	18	74.4	80
3	869740	JK	57	MALE	LUDHIANA	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	21.5	2+	140/70	98	97	16	65	74
4	98136	J	28	MALE	LUDHIANA	PEDAL EDEMA	NONE	CKD	CKD IV	24	2+	130/90	90	97	18	160	186
5	433900	DD	53	FEMALE	PATHANKOT	SOB PEDAL EDEMA	DM	DM CKD	CKD IV	15	2+	110/90	86	98	18	73	97
6	1426281	BS	48	MALE	JALANDHAR	ABDOMINAL PAIN	HTN NEPHROLITHIASIS	HTN CKD	CKD V	11	3+	120/90	89	94	18	70	87
7	13031521	PS	28	MALE	SAMBA	PEDAL EDEMA	HTN	HTN CKD	CKD IV	16	2+	130/70	84	97	20	67	69
8	1298042	BS	60	MALE	FARIDKOT	FEVER	HTN CLD CKD	HTN CLD CKD	CKD IV	16	3+	110/90	98	97	21	40	64
9	1421999	M	52	FEMALE	MOGA	UNCONTROLLED DIABETES	DM	DM CKD	CKD III	34	1+	120/90	84	98	18	25	38
10	104819	HS	20	MALE	LUDHIANA	FATIGUE	NONE	CKD	CKD III	40	2+	120/90	90	97	20	150	159
11	1433023	BS	52	MALE	LUDHIANA	SOB	DM	DM CKD	CKD IV	17	2+	110/70	82	98	18	67.2	84
12	232328	KK	80	FEMALE	MOGA	PEDAL EDEMA SOB	HTN DM	DM HTN CKD	CKD III	38	2+	130/90	90	97	18	63.9	78.1
13	1291610	BS	76	MALE	MOGA	GENERALISED WEAKNESS	HTN OLD CVA	HTN OLD CVA CKD	CKD IV	20	3+	110/70	82	96	17	79.7	91
14	1473594	JK	65	FEMALE	LUDHIANA	PEDAL EDEMA	DM	DM CKD	CKD IV	16	2+	120/80	97	94	18	58	40
15	576508	BR	57	FEMALE	SBS NAGAR	PEDAL EDEMA	HTN	HTN CKD	CKD IV	18	2+	140/80	74	95	12	79	84
16	1354522	RK	45	MALE	LUDHIANA	SOB	DM HTN ADPKD	DM HTN ADPKD CKD	CKD III	30	2+	120/70	79	97	16	80	84
17	1475223	SK	41	MALE	JAMMU	SOB	NONE	CKD	CKD IV	25	2+	110/70	90	94	16	35	51
18	520429	PK	66	FEMALE	LUDHIANA	PEDAL EDEMA	CKD	CKD	CKD IV	21	2+	120/90	80	96	12	70	59
19	81700	SK	61	FEMALE	LUDHIANA	PEDAL EDEMA SOB	DM HTN	DM HTN CKD	CKD III	52	1+	100/60	64	98	12	42	56
20	1461920	SL	59	FEMALE	JAMMU	UNCONTROLLED BLOOD SUGARS	DM	DM CKD	CKD IV	20	2+	110/70	84	94	14	64	56
21	340015	VR	65	FENALE	JAMMU	SOB PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	22	2+	110/70	80	97	18	38	70
22	1509043	KK	32	FEMALE	BARNALA	FOLLOW UP	DM	DM CKD	CKD IV	22	2+	120/70	74	98	16	56	68
23	1504925	JS	67	MALE	HOSHIARPUR	SOB	DM HTN CAD	DM HTN CAD CKD	CKD IV	18	3+	110/70	80	97	18	70	36
24	1479407	TR	64	FEMALE	JALANDHAR	FOLLOW UP	DM HTN	DM HTN CKD	CKD III	37	2+	110/70	72	97	18	48	28
25	1525749	H	61	MALE	LUDHIANA	FOLLOW UP	DM	DM CKD	CKD IV	17	2+	120/70	80	97	20	56	59
26	1405688	BL	73	MALE	LUDHIANA	COUGH SOB	OBESES DM	DM OBESE CKD	CKD III	45	1+	100/60	68	96	18	46	58
27	1296819	SK	54	FEMALE	LUDHIANA	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD V	13	3+	110/70	86	97	20	60	74
28	1508701	RK	30	FEMALE	LUDHIANA	PEDAL EDEMA	HTN	HTN CKD	CKD IV	25	2+	120/70	80	97	18	88	94
29	351646	AS	57	MALE	FEROZPUR	SOB	DM	DM CKD	CKD IV	28	2+	110/70	84	97	18	95.6	105
30	400217	AK	36	MALE	NAWASAHAR	FOLLOW UP	DM	DM CKD	CKD IV	22	2+	120/90	84	96	16	80	96
31	661311	PR	44	FEMALE	MANSA	BURNING MICTURITION	DM	DM CKD	CKD V	14	4+	110/70	69	97	18	31	49
32	1341129	RS	59	MALE	JAMMU	PEDAL EDEMA SOB	DM HTN	DM HTN CKD	CKD IV	21	4+	110/70	90	96	16	64	68
33	1246807	MS	52	MALE	FEROZPUR	DECREASED SLEEP	DM HTN	DM HTN CKD	CKD IV	28	2+	120/70	80	96	18	72	68
34	1456407	KK	40	FEMALE	LUDHIANA	PEDAL EDEMA	HTN	HTN CKD	CKD IV	23	2+	120/70	78	97	20	64	76
35	1503188	J	60	FEMALE	LUDHIANA	GENERALISED WEAKNESS	CVA	CVA CKD	CKD IV	15	2+	110/70	78	97	20	40	37
36	1329153	SK	62	MALE	LUDHIANA	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	27	1+	110/60	64	94	18	36	44
37	1588561	LS	72	MALE	LUDHIANA	DECRESE URINE PEDAL EDEMA	DM	DMCKD	CKD IV	21	1+	110/70	69	94	17	219	198
38	1579863	DS	70	MALE	LUDHIANA	SOB	DM HTN	DM HTN CKD	CKD IV	20	2+	120/80	76	96	16	33	45
39	1483853	GD	60	FEMALE	JAMMU	SOB PEDAL EDEMA	DM	DM CKD	CKD IV	16	2+	110/70	82	96	18	50	65
40	1557730	AK	60	FEMALE	LUDHIANA	DOE	DM CAD	DM CAD CKD	CKD IV	19	1+	100/60	96	92	18	74	81
41	743309	SP	61	FEMALE	SANGRUR	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	16	2+	110/70	92	96	18	51	64
42	1554331	CS	54	MALE	LUDHIANA	PEDAL EDEMA DECREASE URINE	DM HTN	DM HTN CKD	CKDIV	18	2+	130/90	90	96	21	36	54
43	1599491	RM	63	MALE	LUDHIANA	DOE PEDAL EDEMA	DM HTN CAD	DM HTN CAD CKD	CKD IV	16	2+	110/70	84	96	12	54	48
44	1489733	BK	55	FEMALE	LUDHIANA	COUGH SOB	RA ILD DM	RA ILD DM CKD	CKD IV	17	2+	140/90	90	96	24	57	68
45	241271	RV	56	FEMALE	LUDHIANA	SOB PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	27	1+	110/70	94	98	18	58	61
46	1704476	JK	73	FEMALE	MOGA	DOE	DM	DM CKD	CKD IV	29	1+	120/80	78	96	15	150	159
47	70082	BD	62	MALE	MOGA	PEDAL EDEMA DOE	DM CAD HTN	DM HTN CAD CKD	CKD IV	19	2+	100/60	76	98	18	70	87
48	1513193	MP	56	MALE	LUDHIANA	SOB PEDAL EDEMA	DM CAD HTN	DM CAD CKD	CKD III	38	1+	120/80	90	98	22	67.2	84
49	161160	JL	73	MALE	GURDASPUR	SOB COUGH	DM COPD CAD	DM CAD COPD CKD	CKD IV	26	2+	110/70	90	96	16	48	28
50	25098	SS	61	FEMALE	LUDHIANA	PEDAL EDEMA	DM HTN CAD	DM HTN CAD CKD	CKD IV	25	1+	100/60	78	96	22	56	59

SR.NO	IRON AT 6 MONTH	IRON AT 12 MONTH	CALCIUM AT 0 MONTH	CALCIUM AT 3 MONTHS	CALCIUM AT 6 MONTHS	CALCIUM AT 12 MONTHS	FERRITIN AT 0 MONTHS	FERRITIN AT 3 MONTHS	FERRITIN AT 6 MONTHS	FERRITIN AT 12 MONTHS	PHOSPHORUS AT 0 MONTH	PHOSPHORUS AT 3 MONTH
1	48	64	7.2	7.8	8.1	8.5	156	165	189	230	5.72	4.98
2	94	110	8.2	8.4	8.6	8.5	134	163	174	207	5.2	4.6
3	114	164	7	7.4	7.6	8	550	670	710	748	8.52	6.79
4	191	174	9.1	9.6	9.7	8.8	986	1101	946	1216	4.8	4.3
5	110	148	6.6	7	7.6	8.5	468	494	526	568	6.4	5.6
6	106	138	8.5	8.9	9.1	8.9	486	492	564	586	5.5	4.9
7	81	98	7.9	7.7	8.2	8.7	287	291	162	215	4.9	4.4
8	98	144	8.8	9	9.4	9.7	407	104.8	168	247	5.9	5.19
9	74	98	8.1	8.4	8.9	9.2	986	684	972	819	5.2	4.7
10	171	246	8.8	9.4	9.6	10	748	541	469	517	6.4	5.29
11	91	127	9	9.2	9.6	9.8	145	194	261	224	4.84	4.41
12	88	94.6	9.5	9.73	9.9	9.6	123	141	184	217	5.8	5.1
13	110	143	9	9.7	9	9.2	190	194	241	229	5	4.5
14	43	46	9	9	9.3	9.5	167	777	1309	4636	5.3	5.1
15	78	91	9.3	9.6	8	8.9	700	610	748	818	4.9	4.4
16	86	94	7.3	7.6	8.7	9.1	40	56	141	192	5.6	5.1
17	64	69	7	7.4	7.9	8.6	415	486	510	474	6.3	4.9
18	51	68	7.5	7.8	8.1	8.4	654	784	890	1104	4.6	4.3
19	68	98	9	9.4	9.1	8.9	20	48	76	112	5.2	4.6
20	90	177	7.2	8.1	8.2	8.6	440	197	334	277	6.2	5.8
21	96	141	9	9.8	9.3	9.2	167	591	536	491	5.3	4.8
22	76	84	8.7	9.2	9.2	9.3	60	100	118	162	8.52	4.6
23	58	74	9	9.1	8.8	8.6	24	55	82	119	7.2	5.8
24	56	64	8.8	11	9.9	8.7	54	57	59	68	5.7	3.6
25	64	78	8.6	8.7	8.9	8.5	25	54	76	86	5.8	4.9
26	65	94	8.8	9	9.2	9.1	96	101	128	152	5.1	4.6
27	84	102	11	11.2	10.8	11.11	102	147	256	294	6.3	5.4
28	109	121	7.5	7.8	8.4	8.9	23	38	47	54	5.2	4.9
29	117	130	8.5	8.8	8.7	9.1	165	178	191	207	5.6	4.9
30	114	136	6.9	7.4	7.8	8.2	630	601	584	549	5.5	4.7
31	58	64	7.8	8.2	8.5	8.9	41	54	76	68	6.1	5.3
32	75	90	8.2	8.8	9.5	9.9	436	490	551	550	4.9	4.5
33	76	81	9.4	9.2	8.9	8.6	190	268	374	409	5.9	5.1
34	89	103	10	9.8	9.6	9.2	300	330	351	368	5.3	4.9
35	50	64	6.3	6.6	7.7	8.3	210	170	98	76	5.3	4.3
36	56	64	9	9.1	9.3	9.4	97	135	168	174	6.4	5.4
37	164	120	8.8	8.6	9	9.6	309	291	264	245	5.8	4.7
38	74	68	9.3	9.4	9.8	10.1	578	584	464	392	6.7	5.6
39	74	81	10	9.6	9.2	9.8	127	149	158	193	6.5	5.8
40	90	106	9.9	8.6	9.1	10	148	144	136	161	5.7	4.9
41	72	81	8.3	8.4	8.7	9.1	94	89	84	79	5.9	5.1
42	61	67	8.9	9.1	9.3	9.7	112	146	290	619	6	5.4
43	64	72	9.2	8.9	8.6	9.4	240	261	274	254	5.9	5.3
44	74	79	7.1	7.4	7.9	8.2	484	444	596	618	7.1	6.1
45	76	89	7.5	7.8	8.2	8.6	291	313	365	501	5.9	5.4
46	171	246	7.8	8.4	9.1	9.4	98	154	224	280	6.4	5.46
47	106	138	7.9	8.2	8.9	8.8	20	45	69	154	5.4	4.9
48	91	127	8.4	8.7	9.1	9.4	86	102	129	228	6.1	5.4
49	56	64	8.1	8.6	9.7	9	54	69	105	168	5.7	4.6
50	64	78	7.9	8.4	9	9.4	74	96	112	154	6.4	5.12

SR.NO	PHOSPHORUS AT 6 MONTH	PHOSPHORUS AT 12 MONTHS	HEMOGLOBIN AT 0 MONTH	HEMOGLOBIN AT 3 MONTH	HEMOGLOBIN AT 6 MONTH	HEMOGLOBIN AT 12 MONTH	PARATHYROID LEVELS AT 0 MONTH	PARATHYROID AT 3 MONTHS	PARATHYROID AT 6 MONTHS	PARATHYROID AT 12 MONTHS	ALKALINE PHOSPHATE AT 0 MONTH
1	4.12	3.67	8.9	9.1	9.5	9.9	1029	980	950	910	17
2	3.8	3.5	8.6	8.9	9.1	9.6	569	540	555	560	44
3	5.6	4.4	9.6	9.80	10.2	10.6	428	450	474	490	38
4	3.8	3.3	8.8	8.9	9.6	10.6	642	616	580	540	337
5	4.5	3.4	8.6	8.8	9.5	9.9	1019	1121	1300	1391	140
6	3.9	3.2	7.8	8.2	8.6	9.6	118	124	149	154	202
7	3.9	3.7	9.3	9.3	10.1	10.5	188	227	313	427	540
8	4.17	3.98	8.2	8.6	8.8	9.4	274	568	848.7	654	272
9	4.3	3.78	9.8	9.6	10.1	10.7	842	748	794	814	151
10	4.5	3.4	9.2	9.6	9.7	10.1	550	310	241	183	140
11	3.97	3.16	8.9	9.4	9.6	9.8	203	248	291	341	101
12	4.4	3.9	11.3	11.4	10.6	11	131	119	106	112	98
13	4	3.8	9	9.2	9.6	9.9	79	77	71	75	100
14	4.4	3.8	8.4	8.8	9.1	9.6	236	220	194	171	125
15	4.1	3.8	9.9	10	9.00	9.8	782	810	860	888	188
16	4.7	4.3	9.8	9.6	9.9	9.7	481	491	476	488	175
17	4.15	3.6	9	9.2	9.3	9.5	538	434	410	394	102
18	3.9	3.6	9.2	9.4	9.7	9.8	668	516	449	287	102
19	3.5	2.7	7.4	7.8	8.1	8.4	98	81	74	79	117
20	4.1	3.3	7.4	7.8	8.2	8.6	454	354	286	186	135
21	4.4	3.5	9.4	10.1	10.6	10.4	236	264	130	68	125
22	4.5	3.4	9.9	10.4	10.6	10.5	215	158	123	110	89
23	4.1	3.3	8	8.2	8.4	8.3	17	28	48	44	100
24	3.3	2.7	9.5	10.2	10.3	10.5	78.6	102	141	126	58
25	4.6	4.3	9.1	9.4	9.7	9.6	415	510	549	568	85
26	4.3	3.8	10.4	10.6	10.2	10.5	96	104	116	109	172
27	4.1	3.7	9.6	9.8	10.2	10.5	31	21	27	35	74
28	4.3	3.1	8.2	8.5	8.8	9.6	427	440	414	398	84
29	4.2	3.9	10	10-Apr	10.5	10.9	273	240	210	236	90
30	4	3.7	8.8	9.1	9.5	9.8	1257	1009	981	867	90
31	4.2	3.7	7.9	8.3	8.5	8.9	698	684	661	649	150
32	3.7	3.4	7.8	8.6	10	11.9	77	67	58	41	94
33	4.5	3.8	8.3	8.5	8.8	9.2	56	61	69	76	94
34	4.3	3.9	9.7	9.8	10	10.4	366	340	329	298	86
35	3.5	3.4	6.6	7.2	7.6	8.2	1057	896	666	859	67
36	4.4	3.7	9	9.4	9.6	9.9	86	90	96	102	100
37	4.3	3.8	11	10.6	10.8	10.5	42	48	54	61	124
38	4.5	3.6	5.8	6.2	6.8	9	182	164	176	194	194
39	4.6	3.9	8.1	8.4	8.9	9.2	50	56	61	72	90
40	4.3	4	7.7	8.1	8.6	9.1	50	56	64	70	91
41	4.4	3.8	9.6	9.7	10.1	10.5	142	110	96	75	110
42	4.1	3.5	9.1	9.3	9.7	10.1	244	261	254	210	146
43	4.5	4.1	9.6	9.9	10.1	10	42	54	59	64	120
44	5.4	4.2	8.2	8.8	9	9.4	414	449	468	510	160
45	4.8	3.5	7.6	8.1	8.7	9.8	573	485	490	416	140
46	4.23	3.16	8.9	9.4	9.6	9.8	148	218	291	305	101
47	4.2	3.8	8.1	8.5	8.9	10	446	506	549	586	100
48	3.9	3.2	7.8	8.5	9.1	10.4	118	156	189	209	112
49	3.3	3	7.5	8.2	8.9	10.5	78.6	145	186	126	58
50	4.35	3.4	7.2	8.4	9.2	10.1	450	310	287	221	140

SR.NO	ALKALINE PHOSPHATE AT 3 MONTH	ALKALINE PHOSPHATE 6 MONTHS	ALKALINE PHOSPHATE AT 12 MONTHS	TIBC AT 0 MONTHS	TIBC AT 3 MONTHS	TIBC AT 6 MONTHS	TIBC AT 12 MONTHS	TRANSFERRIN SATURATION AT 0 MONTH	TRANSFERRIN SATURATION AT 3 MONTH	TRANSFERRIN SATURATION AT 6 MONTH	TRANSFERRIN SATURATION AT 12 MONTH
1	36	68	90	408	385	360	345	3	8	13	18
2	60	61	52	260	241	198	160	28	33	47	68
3	60	64	58	413	402	386	310	15	18	29	52
4	290	210	160	168	154	141	160	59	73	79	48
5	131	110	94	266	250	310	298	27	38	45	49
6	196	164	145	384	340	260	280	18	25	40	49
7	360	217	188	455	364	280	291	14	18	28	33
8	212	194	168	216	240	316	301	18	26	31	47
9	110	98	60	297	280	252	268	8.4	13.5	29	36
10	109	98	74	350	339	276	220	43	46	61	73
11	68	40	57	273	261	215	276	24.6	32	42	46
12	81	69	48	411	374	316	284	15.5	20	27	33
13	91	86	64	298	264	249	283	26	34	44	50
14	95	122	113	320	206	210	146	18	19.4	20	31.5
15	149	116	74	234	216	191	211	33	38	40	43
16	161	115	109	380	364	310	249	21	23	27	37
17	66	54	78	321	307	386	264	11	16	22.3	26
18	94	78	68	224	205	149	140	31	26	34	48
19	98	86	81	400	367	287	210	10	15	23	46
20	140	94	112	212	220	282	356	30	25	31	49
21	172	158	146	470	272	321	294	8.2	26	29	47
22	90	105	96	300	340	312	298	18	20	25	28
23	72	70	62	220	320	276	282	31	11	21	26
24	64	78	84	252	316	284	216	19	9	19	29
25	82	76	69	358	310	297	268	16	19	21	23
26	148	126	94	284	262	249	210	16	22	26	44
27	70	64	58	269	240	246	219	22	30	34	46
28	60	72	78	308	294	286	265	28	31	38	45
29	86	110	105	292	264	249	210	32	39	46	61
30	84	76	72	175	190	216	241	45	50	52	56
31	146	134	116	297	261	248	264	10	18	23	24
32	90	100	84	229	250	262	258	28	27	28	32
33	86	78	71	294	280	264	256	24	24	28	31
34	94	99	104	349	310	289	264	18	24	30	39
35	74	76	80	290	228	239	210	13	16	20	30
36	80	74	68	220	240	258	232	16	18	21	27
37	131	98	64	235	238	254	216	93	66	64	55
38	161	131	68	269	298	251	241	12	15	29	28
39	68	73	51	357	364	378	316	14	17	19	25
40	86	74	71	395	360	314	286	18	22	28	35
41	98	78	64	187	194	210	248	27	32	34	32
42	130	112	64	181	199	240	268	19	27	25	25
43	102	94	74	325	360	378	390	16	13	17	18
44	139	106	94	291	264	220	196	19	25	33	40
45	112	98	64	288	272	256	211	20	22	29	42
46	74	65	57	350	339	276	220	43	46	61	73
47	90	87	67	384	340	260	280	18	25	40	49
48	167	179	145	273	261	215	276	24.6	32	42	46
49	76	88	90	252	316	284	216	19	9	19	29
50	112	90	78	358	310	297	268	16	19	21	23

SR.NO	Serum Bone Specific Alkaline Levels (if required) AT O MONTH	Serum Bone Specific Alkaline Levels (if required) AT 3 MONTH	Serum Bone Specific Alkaline Levels (if required) AT 6 MONTH	Serum Bone Specific Alkaline Levels (if required) AT 12 MONTH
1	NA	NA	NA	NA
2	NA	NA	NA	NA
3	NA	NA	NA	NA
4	NA	NA	NA	NA
5	NA	NA	NA	NA
6	NA	NA	NA	NA
7	NA	NA	NA	NA
8	NA	NA	NA	NA
9	NA	NA	NA	NA
10	NA	NA	NA	NA
11	NA	NA	NA	NA
12	NA	NA	NA	NA
13	NA	NA	NA	NA
14	NA	NA	NA	NA
15	NA	NA	NA	NA
16	NA	NA	NA	NA
17	NA	NA	NA	NA
18	NA	NA	NA	NA
19	NA	NA	NA	NA
20	NA	NA	NA	NA
21	NA	NA	NA	NA
22	NA	NA	NA	NA
23	NA	NA	NA	NA
24	NA	NA	NA	NA
25	NA	NA	NA	NA
26	NA	NA	NA	NA
27	NA	NA	NA	NA
28	NA	NA	NA	NA
29	NA	NA	NA	NA
30	NA	NA	NA	NA
31	NA	NA	NA	NA
32	NA	NA	NA	NA
33	M	NA	NA	NA
34	NA	NA	NA	NA
35	NA	NA	NA	NA
36	NA	NA	NA	NA
37	NA	NA	NA	NA
38	NA	NA	NA	NA
39	NA	NA	NA	NA
40	NA	NA	NA	NA
41	NA	NA	NA	NA
42	NA	NA	NA	NA
43	NA	NA	NA	NA
44	NA	NA	NA	NA
45	NA	NA	NA	NA
46	NA	NA	NA	NA
47	NA	NA	NA	NA
48	NA	NA	NA	NA
49	NA	NA	NA	NA
50	NA	NA	NA	NA

SR.NO	MRD NO	NAME	AGE	SEX	CITY	CHIEF COMPLAINS	COMORBIDITIES (IF ANY)	DIAGNOSIS	CATEGORY	GFR	ALBUMIN	BP	HR	SPO2	RR	IRON AT 0 MONTH	IRON AT 3 MONTH	IRON AT 6 MONTH
1	1106578	MS	79	MALE	MOHALI	CHEST DISCOMFORT	CAD DM HTN	CAD DM HTN CKD	CKD IV	21	2+	110/70	82	97	22	37	77	60
2	1540693	L	41	MALE	FEROZPUR	FOLLOW UP	NONE	CKD	CKD IV	21	1+	120/70	80	97	18	65.5	69	71
3	1533335	NC	19	MALE	HOSHIARPUR	SOB PEDAL EDEMA	NONE	CKD	CKD III	35	1+	120/70	88	98	18	25	28	32
4	1519800	RL	70	MALE	SANGRUR	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD V	14	2+	110/70	80	97	18	16	24	29
5	1393618	PS	67	MALE	LUDHIANA	SOB	DM	DM CKD	CKD V	13	2+	110/70	80	97	16	20.4	22.4	27
6	1525172	SR	52	FEMALE	FARIDKOT	BURNING MICTURITION	DM	DM CKD	CKD V	13	2+	130/70	88	98	20	35.9	39	43
7	1545508	AP	56	MALE	MOGA	DECRESE URINE OUTPUT	DM HTN	DM HTN CKD	CKD V	13	2+	120/70	88	97	18	167	141	112
8	554203	HS	54	MALE	LUDHIANA	FEVER COUGH	HTN	HTN CKD	CKD V 12	12	2+	120/60	90	96	19	36	39	41
9	1543060	PK	62	FEMALE	KANGRA	PEDAL EDEMA	DM	DM CKD	CKD IV	15	2+	100/70	72	98	18	15	19	23
10	1518227	JK	53	FEMALE	MOGA	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	16	2+	120/90	98	97	16	70	64	45
11	1527173	PS	80	MALE	LUDHIANA	DECRESE URINE OUTPUT	DM	DM CKD	CKD IV	17	2+	120/90	78	96	22	50	54	62
12	1530992	MS	63	MALE	JAMMU	PEDAL EDEMA	DM CAD	DM CAD CKD	CKD IV	19	1+	130/70	84	97	20	51	56	62
13	1529453	BK	57	FEMALE	ROPAR	SOB	DM HTN	DM HTN CKD	CKD IV	16	2+	110/70	80	96	18	151	137	112
14	1541735	D	39	MALE	JALANDHAR	SOB	DM	DM CKD	CKD IV	17	3+	120/80	80	97	18	34	39	47
15	1347220	BS	36	MALE	LUDHIANA	GENERALISED WEAKNESS	HTN OLD CVA	HTN OLD CVA CKD	CKD IV	17	2+	120/70	78	98	20	70	79	83
16	944923	NK	59	FEMALE	SBS NAGAR	DECRESE URINE OUTPUT	DM HTN OSA	DM HTN OSA CKD	CKD IV	17	2+	110/70	82	97	20	54	51	47
17	1245432	RS	66	MALE	BARNALA	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	17	2+	120/70	84	97	18	70	74	79
18	1073465	SK	55	FEMALE	MOGA	BURNING MICTURITION	ADPKD	ADPKD CKD	CKD IV	19	2+	110/70	80	96	18	70	65	51
19	1374655	TS	43	MALE	AMRITSAR	PEDAL EDEMA	DM HTN HFREF	CDM HTN HFREF CKD	CKD III	53	2+	130/70	92	94	22	44	68	96
20	1443998	NS	70	MALE	SANGRUR	SOB PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	27	2+	100/70	74	96	18	38	43	47
21	1442648	RS	49	MALE	HOSHIARPUR	SOB	DM CAD	DM CAD CKD	CKD IV	18	1+	110/60	92	97	22	28	33	39
22	839129	S	50	FEMALE	KAPURTHALA	PEDAL EDEMA	DM	DM CKD	CKD IV	26	2+	130/90	86	97	18	21	28	36
23	1138879	N	68	MALE	KARNAL	LOWER GI BLEED	DM HTN HEMARRHOIDS	DM HTN HEMARRRHOIDS	CKD IV	24	1+	100/70	68	95	23	45	48	36
24	1269031	I	63	MALE	JALANDHAR	PEDAL EDEMA SOB	DM	DM CKD	CKD IV	23	2+	110/70	94	98	18	30	32	35
25	1277208	S	70	FEMALE	LUDHIANA	SOB	DM	DM CKD	CKDIV	18	1+	100/60	79	92	28	21	25	29
26	1339048	K	58	FEMALE	LUDHIANA	SOB PEDAL EDEMA	HTN	HTN CKD	CKDIV	24	2+	110/70	72	94	24	50	43	37
27	1444567	BR	75	FEMALE	LUDHIANA	SOB	DM HTN	DM HTN CKD	CKDIV	17	2+	90/70	64	92	12	16	19	24
28	1445366	JS	47	MALE	HOSHIARPUR	FOLLOW UP	NONE	CKD	CKDIII	42	1+	130/70	80	97	16	135	94	38
29	1429235	SS	60	MALE	LUDHIANA	PEDAL EDEMA	HTN	HTN CKD	CKDIV	27	2+	120/60	90	97	18	100	89	76
30	1509622	N	59	FEMALE	JAMMU	DECRESE URINE OUTPUT	DM HTN	DM HTN CKD	CKD IV	28	1+	110/70	84	94	18	21	26	29
31	1339618	PS	68	MALE	LUDHIANA	EPIGASTRIC DISCOMFORT SOB	DM HTN CAD	DM HTN CAD CKD	CKD IV	22	1+	130/60	94	96	12	21.9	31	47
32	1302328	SB	67	FEMALE	KAPURTHALA	PEDAL EDEMA SOB	RA HTN	RA HTN CKD	CKD IV	19	1+	130/70	88	98	16	48	36	54
33	1582955	JS	47	MALE	LUDHIANA	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD III	33	1+	140/70	84	94	18	114	93	54
34	1583516	HS	45	MALE	LUDHIANA	SOB	DM HTN	DM HTN CKD	CKD IV	24	1+	130/70	79	94	18	29	36	54
35	648232	SK	25	MALE	JAMMU	PEDAL EDEMA	NONE	CKD	CKD IV	20	1+	130/90	90	98	14	87	72	66
36	1603036	GS	45	MALE	LUDHIANA	SOB	DM HTN	DM HTN CKD	CKD IV	25	1+	140/90	94	94	18	67	72	76
37	1574375	JK	50	FEMALE	MALER KOTLA	PEDAL EDEMA	DM	DM CKD	CKD IV	20	2+	130/70	90	94	18	94	68	51
38	1608580	SR	65	FEMALE	FAZILKA	SOB PEDAL EDEMA	DM HTN CAD	DM HTN CAD CKD	CKD V	11	2+	140/70	78	94	18	149	76	54
39	1191710	BA	62	FEMALE	LUDHIANA	DOE	DM CAD	DM CAD CKD	CKD IV	18	1+	110/90	90	94	18	86	70	56
40	1613021	SS	39	MALE	SANGRUR	UNCONTROLLED BP	HTN	HTN CKD	CKD IV	17	1+	140/70	90	94	18	54	68	87
41	1611360	GS	62	MALE	TARAN TARAN	PEDAL EDEMA DECREASE URIN	DM HTN	DM HTN CKD	CKD III	32	1+	150/90	90	94	20	119	78	61
42	1609637	BK	55	FEMALE	FARIDKOT	PEDAL EDEMA SOB	DM HTN	DM HTN CKKD	CKD IV	17	2+	150/90	90	98	18	29	35	47
43	1590441	P	59	FEMALE	LUDHIANA	PEDAL EDEMA	DM	DM CKD	CKDIV	22	1+	140/70	90	94	18	68	74	51
44	1588900	NS	66	MALE	MOGA	DECRESE URINE OUTPUT	DM CAD	DM CAD CKD	CKD IV	26	1+	110/70	74	94	18	74	98	116
45	129708	SJ	52	FEMALE	LUDHIANA	PEDAL EDEMA	DM HTN	DM HTN CKD	CKD IV	19	2+	130/70	90	94	16	27	33	53
46	1282687	NG	62	FEMALE	LUDHIANA	PEDAL EDEMA	DM	DM CKD	CKD IV	20	1+	120/80	84	94	16	54	68	75
47	735593	SK	64	FEMALE	MUKTSAR	FEVER COUGH SOB	DM CAD COPD	DM CAD COPD CKD	CKD IV	17	2+	140/90	90	98	14	69	87	134
48	1526711	S	55	FEMALE	TARAN TARAN	SOB	HTN CAD EF 48%	HTN CAD CKD	CKD IV	17	1+	130/90	102	94	18	27	51	74
49	1518467	SK	35	FEMALE	LUDHIANA	PEDAL EDEMA	NONE	CKD	CKD IV	28	1+	130/90	94	96	18	77	66	60
50	1002860	V	63	MALE	LUDHIANA	SOB	DM HTN	DM HTN CKD	CKD IV	19	1+	130/70	94	92	18	69	98	134

SR.NO	IRON AT 12 MONTH	CALCIUM AT 0 MONTH	CALCIUM AT 3 MONTHS	CALCIUM AT 6 MONTHS	CALCIUM AT 12 MONTHS	FERRITIN AT 0 MONTHS	FERRITIN AT 3 MONTHS	FERRITIN AT 6 MONTHS	FERRITIN AT 12 MONTHS	PHOSPHORUS AT 0 MONTH	PHOSPHORUS AT 3 MONTH	PHOSPHORUS AT 6 MONTH
1	84	7.1	7.6	7.9	8.14	400	501	872	764	6.7	5.6	4.5
2	74	7.6	7.9	8.3	8.6	293	274	286	310	6.2	5.4	4.3
3	30	7.9	8.1	8.3	8.6	56	54	61	59	7.1	5.6	4.57
4	34	8.38	8.1	7.9	8.4	152	146	164	158	5.8	5.01	4.46
5	32.5	7.48	7.42	7.9	8.1	593	568	449	328	5.7	5.1	4.39
6	57	7.8	7.9	8.1	8.6	343	368	359	371	6.3	5.9	4.7
7	96	7.2	7.3	7.5	7.9	1085	996	941	978	6.7	5.3	4.4
8	47	7.8	7.9	8.1	8.3	490	510	474	456	5.7	5.1	4.4
9	29	7.9	8.1	8.4	8.2	211	241	268	291	5.7	5	4.36
10	30	8	7.8	7.6	7.4	428	494	551	619	6.8	5.1	4.6
11	69	7.5	7.6	7.8	8.4	415	546	596	648	5.4	4.7	4.2
12	79	8.7	8.9	8	8.4	124	151	179	210	4.7	4.3	3.7
13	98	10	9.8	9.5	9.1	590	616	674	651	5.6	5.1	4.4
14	54	7.4	7.6	7.7	7.9	198	210	244	271	4.8	4.3	3.9
15	87	9	8.9	8.4	8.6	50	62	68	71	6.2	5.4	4.6
16	43	8	8.2	7.9	7.6	41	55	56	111	4.7	4.4	4.2
17	83	9.5	8.9	8.7	8.2	294	276	254	248	65.2	5	4.3
18	35	8.9	9	8.7	8.5	50	30	47	59	6.5	5.4	4.6
19	108	7.9	7.7	8.1	8.4	679	550	430	435	7.1	6.4	5
20	51	7.5	7.8	7.9	8.1	233	264	271	256	5.3	4.7	3.9
21	47	7.2	7.5	7.9	8.4	95	110	117	129	6.5	5	4.3
22	42	6	6.6	7.2	7.9	116	141	156	194	7.2	6	5.1
23	28	7.2	7.5	7.8	8.1	54	59	61	64	5.9	5.3	4.6
24	39	7.2	7.3	7.4	7.8	593	570	548	521	8.2	6.41	5.5
25	35	10.9	9.7	9.3	9	714	684	660	675	7.6	6.1	5.3
26	31	8.5	8.4	8.1	7.9	754	710	648	694	4.5	4.1	3.9
27	29	8.6	8.9	9.2	8.7	409	398	378	326	5.5	5	4.3
28	25	8.9	8.5	8.3	7.8	450	448	431	425	5.1	4.6	3.9
29	54	8.3	7.7	7.9	8.6	150	164	170	186	6.2	5.8	5.4
30	33	8.1	7.9	7.7	8.3	212	242	258	274	6.4	6	5.1
31	58	10.14	10.4	10.8	9.6	85	89	200	126	6.1	5.3	4.6
32	51	9.1	9.4	9.5	9.7	141	156	123	169	5.4	4.9	4.3
33	24	8.7	8.6	8.1	8.9	445	461	413	368	5	4.4	3.9
34	76	8.7	8.9	9.1	9.4	641	610	598	564	5.5	4.9	4
35	48	9.1	8.7	8.3	7.6	221	244	268	210	5.8	5	4.4
36	81	9.9	9.7	9.3	8.7	5522	514	551	568	5.5	4.9	4.3
37	36	9.6	9.3	8.9	8.7	481	4664	431	419	6.5	5.1	4.3
38	34	7.4	7.6	7.9	8.2	449	410	378	389	6.4	5.6	4.6
39	44	8.1	8.2	8.4	8.8	96	114	146	158	5	4.6	3.8
40	114	9.6	9.4	9.1	8.8	456	468	480	540	5.7	5.3	4.7
41	54	9.7	9.9	9.5	8.9	617	541	568	510	7.6	6	5.3
42	64	8.7	8.8	9	9.3	346	368	391	410	6.1	5.3	4.5
43	84	7.7	7.9	8.2	8.5	746	714	684	658	6	5.5	4.2
44	114	7.7	8.6	8.8	8.5	641	692	768	546	6.1	5.5	4.3
45	68	7.9	8.4	8.6	8.7	120	180	214	244	6.9	6	4.6
46	96	7.8	8.2	8.3	8.5	58	69	78	110	5.6	4.8	3.5
47	152	7.5	7.7	7.9	8.3	564	590	603	684	5.8	5.1	4.3
48	89	7.5	7.7	8.2	8.6	161	340	494	549	5.6	5	4.4
49	64	7.1	7.6	7.9	8.5	501	564	872	890	6.1	5	4.5
50	158	7.6	7.9	8.2	8.6	603	564	590	650	6.1	5.5	4.6

SR.NO	PHOSPHORUS AT 12 MONTHS	HEMOGLOBIN AT 0 MONTH	HEMOGLOBIN AT 3 MONTH	HEMOGLOBIN AT 6 MONTH	HEMOGLOBIN AT 12 MONTH	PARATHYROID LEVELS AT 0 MONTH	PARATHYROID AT 3 MONTHS	PARATHYROID AT 6 MONTHS	PARATHYROID AT 12 MONTHS	ALKALINE PHOSPHATE AT 0 MONTH
1	4.1	8.1	8.5	8.8	8.9	242	490	550	594	83
2	3.9	6.1	6.5	6.8	7.1	495	454	476	510	111
3	3.89	7.4	7.6	7.7	7.9	640	565	714	668	91
4	3.76	7.4	7.5	7.7	8.1	990	1004	1072	968	133
5	3.76	5.7	6.4	6.6	6.9	851	816	768	794	78
6	3.6	8.5	8.3	8.6	8.7	230	246	268	271	82
7	3.7	8	8.1	8.3	8.5	320	364	379	384	100
8	3.8	9	8.8	8.3	8.5	317	346	367	381	258
9	3.51	7.2	7.4	7.7	7.9	876	898	916	945	72
10	4.1	9	8.8	8.5	8.3	300	290	340	312	90
11	3.7	9	8.8	8.1	8.5	990	871	844	791	85
12	3.2	7.8	8.1	7.7	8.3	178	210	236	274	83
13	4.1	9.2	8.9	8.6	8.5	3472	2968	1456	1049	779
14	3.4	7.2	7.5	7.7	8.1	550	468	476	496	58
15	4.1	10.9	10.7	10.3	9.8	349	356	369	383	92
16	3.7	8.7	8.9	8.5	8.6	329	440	561	675	136
17	3.5	10.8	10.4	9.8	9.7	424	452	479	496	90
18	4	10.8	9.4	9	8.6	912	880	764	678	62
19	4.4	8.3	8.4	8.6	8	137	148	150	161	113
20	3.2	8	7.9	7.7	7.5	352	340	310	289	86
21	3.7	8.9	8.7	8.3	8.4	240	258	264	270	87
22	4.2	7.4	7.6	7.9	8.1	235	248	259	264	116
23	3.8	7.6	7.7	7.9	8	592	570	548	536	210
24	4.4	8.4	8.1	7.9	8	942	968	848	810	77
25	4.2	8.7	8.8	8.5	9	547	514	536	578	140
26	3.4	8.1	7.7	7.8	8.2	352	368	310	292	99
27	3.6	7.4	7.6	7.7	7.9	345	354	368	376	92
28	2.5	10.8	10.4	10.1	9.4	915	928	936	954	120
29	4.5	10.2	9.6	9.2	9.5	373	458	469	474	46
30	4.1	8.1	7.9	8.3	8.4	910	954	964	946	64
31	3.7	8.4	8.1	8.7	8.6	154	174	167	189	109
32	3.8	9.4	9.1	9	9.3	1201	964	958	1013	134
33	3.1	7.6	7.7	7.9	7.8	156	175	168	210	64
34	3.1	10.1	9.6	9.9	10.4	133	140	164	192	116
35	2.7	8.4	8.5	8.1	8.3	954	962	979	981	140
36	3.7	9	8.8	8.5	8.6	307	321	334	368	88
37	3.7	10	9.4	8.6	8.9	694	658	662	586	154
38	3.4	8.3	7.9	8.1	8.4	1134	9986	946	814	110
39	3	7.3	7.4	7.5	7.9	192	217	246	230	43
40	3.8	10	9.4	9.20	9.00	898	876	851	886	145
41	4	8.7	9.4	9	8.9	1314	1210	968	864	96
42	3	8.9	8.5	8.1	8.3	154	168	129	137	94
43	3.6	8.9	9	8.8	8.5	276	248	219	256	104
44	3.2	9.5	10	10.4	10.9	960	981	968	1001	100
45	2.8	8.1	8.4	8.5	8.8	260	298	310	325	118
46	2.3	8.6	9.4	9	8.9	268	240	212	198	168
47	3.8	8	7.6	7.9	8.4	112	114	129	148	176
48	3.2	7.7	7.9	8.4	8.8	498	540	640	580	154
49	3.8	8	8.2	6.6	8.4	480	410	370	440	83
50	3.8	6.5	6.9	7.4	8	81	111	140	180	296

SR.NO	ALKALINE PHOSPHATE AT 3 MONTH	ALKALINE PHOSPHATE 6 MONTHS	ALKALINE PHOSPHATE AT 12 MONTHS	TIBC AT 0 MONTHS	TIBC AT 3 MONTHS	TIBC AT 6 MONTHS	TIBC AT 12 MONTHS	TRANSFERRIN SATURATION AT 0 MONTH	TRANSFERRIN SATURATION AT 3 MONTH	TRANSFERRIN SATURATION AT 6 MONTH	TRANSFERRIN SATURATION AT 12 MONTH
1	87	70	64	199	238	161	142	18	32	37	59
2	90	121	140	278	264	215	246	23	26	33	30
3	60	78	86	441	446	410	368	5.6	6.2	8	8
4	121	96	87	359	401	386	415	4	6	7.5	8
5	109	122	146	196	210	258	294	10.5	10.6	10.4	10.8
6	96	110	138	215	246	278	290	16	15	15.4	19.6
7	94	89	74	188	219	261	296	89	64.5	42	32
8	132	101	89	261	246	278	294	14	16	15	16
9	78	81	86	390	376	345	296	4	5	6	10
10	79	64	58	204	196	179	166	34	32	25	18
11	96	119	141	294	346	310	331	17	15.5	20	21
12	98	140	176	276	310	346	378	18	18	17.9	21
13	592	374	268	286	294	316	368	52	46.5	35	26.6
14	61	67	78	229	246	271	290	15	15	17	18.6
15	89	81	77	300	296	264	247	23	26	31	35
16	90	118	127	190	246	265	224	28	20.7	17.7	19.6
17	110	136	149	300	340	376	391	23	21	21	21.2
18	64	76	90	300	350	384	410	23	18	13	8
19	135	200	165	114	164	208	202	38	41	46	53
20	110	136	148	110	190	231	276	34	22	20	18.4
21	91	94	97	179	190	216	240	15	17.3	18	20
22	94	80	68	223	241	264	286	9	11	13.6	14.6
23	186	174	160	450	428	410	400	10	11	9	7
24	68	94	110	510	485	426	368	6	6.5	8	10.5
25	110	94	80	274	289	298	310	7	8	13	11.2
26	86	79	72	492	480	461	429	10.1	9	8	7
27	84	80	68	325	345	368	374	5	5.5	6.5	7.7
28	94	89	67	410	368	310	172	32	25	12	14.5
29	57	62	69	380	394	410	406	26	22.5	18	13
30	87	88	96	246	213	254	268	8	12	11	12
31	78	64	56	255	228	105	175	8.5	13.5	44.7	34
32	114	87	64	268	292	314	284	17	12	17	18
33	668	40	54	496	468	410	454	23	20	13	5
34	90	64	78	396	364	314	268	7	9.8	17	28.3
35	136	124	110	251	264	281	290	34	27	23	16
36	110	136	164	257	256	210	189	26	30	36	43
37	168	142	96	256	279	314	368	36	24	16	10
38	87	70	68	264	281	368	394	56	27	14.6	8.6
39	56	68	110	468	391	356	374	18	17	15	11
40	119	96	664	490	471	436	396	11	14	19	28
41	84	64	40	449	381	356	287	26	20	17	19
42	110	116	146	251	214	268	346	11	16	17.5	18
43	98	64	40	490	468	384	356	13	15	13	23
44	92	76	60	216	248	291	354	34	39	39	40
45	99	125	146	238	251	266	310	11	13	20	21
46	192	132	110	296	270	248	210	18	25	30	45
47	140	119	89	247	227	312	489	27	38	42	31
48	114	90	68	280	210	153	226	9	24	48	39
49	73	87	90	238	177	161	135	32	37	37	47
50	220	180	164	290	252	240	198	23	38	55	53

SR.NO	Serum Bone Specific Alkaline Levels (if required) AT O MONTH	Serum Bone Specific Alkaline Levels (if required) AT 3 MONTH	Serum Bone Specific Alkaline Levels (if required) AT 6 MONTH	Serum Bone Specific Alkaline Levels (if required) AT 12 MONTH
1	NA	NA	NA	NA
2	NA	NA	NA	NA
3	NA	NA	NA	NA
4	NA	NA	NA	NA
5	NA	NA	NA	NA
6	NA	NA	NA	NA
7	NA	NA	NA	NA
8	NA	NA	NA	NA
9	NA	NA	NA	NA
10	NA	NA	NA	NA
11	NA	NA	NA	NA
12	NA	NA	NA	NA
13	NA	NA	NA	NA
14	NA	NA	NA	NA
15	NA	NA	NA	NA
16	NA	NA	NA	NA
17	NA	NA	NA	NA
18	NA	NA	NA	NA
19	NA	NA	NA	NA
20	NA	NA	NA	NA
21	NA	NA	NA	NA
22	NA	NA	NA	NA
23	NA	NA	NA	NA
24	NA	NA	NA	NA
25	NA	NA	NA	NA
26	NA	NA	NA	NA
27	NA	NA	NA	NA
28	NA	NA	NA	NA
29	NA	NA	NA	NA
30	NA	NA	NA	NA
31	NA	NA	NA	NA
32	NA	NA	NA	NA
33	NA	NA	NA	NA
34	NA	NA	NA	NA
35	NA	NA	NA	NA
36	NA	NA	NA	NA
37	NA	NA	NA	NA
38	NA	NA	NA	NA
39	NA	NA	NA	NA
40	NA	NA	NA	NA
41	NA	NA	NA	NA
42	NA	NA	NA	NA
43	NA	NA	NA	NA
44	NA	NA	NA	NA
45	NA	NA	NA	NA
46	NA	NA	NA	NA
47	NA	NA	NA	NA
48	NA	NA	NA	NA
49	NA	NA	NA	NA
50	NA	NA	NA	NA

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The Principal
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Subject:: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 25.09.2023 has approved the plan of thesis of **Nirmal Singh**, a student of your college for **MD General Medicine** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Comparative efficacy of ferric citrate and sevelamer carbonate in patients of non - dialysis dependent chronic kidney disease .

Supervisor
Dr. Amit Bery
Assoc. Professor
Dept. of General Medicine

Co-Supervisor:-
Dr. Preet Mohinder Singh
Assoc. Professor
Dept. of Nephrology

The student may submit the thesis in triplicate alongwith the plan in triplicate also, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

23/12/2023
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED IN

PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MD

In

GENERAL MEDICINE

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

JUNE, 2022

DR NIRMAL SINGH

DEPARTMENT OF GENERAL MEDICINE
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON - DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE
For the degree of	MD General Medicine
Name of the candidate	Dr Nirmal Singh
Supervisor	Dr Amit Bery, Associate Professor, Department of General Medicine, DMCH, Ludhiana
Co-Supervisor	Dr. Preet Mohinder Singh, Associate Professor, Department of Nephrology, DMCH, Ludhiana
Institution	Dayanand Medical College and Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Chronic kidney disease encompasses a spectrum of pathophysiology processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate. Chronic kidney disease is staged by KDIGO (kidney disease improving global outcome) classification when renal failure progress stage – III (GFR - 45-59 ml / min / 1.73 m2) to stage - V (GFR < 15 ml / min / 1.73 m2) is the class requiring phosphate binders and may or may not require dialysis. Ferric citrate is a drug initially introduced as a phosphate binder in dialysis dependent chronic kidney disease patient, but recent study have showed that that it can also be used in non-dialysis-dependent chronic kidney disease patients. On the other hand sevelamer carbonate is an improved buffered form of sevelamer hydrochloride developed for the treatment of hyperphosphatemia in patient of non-dialysis dependent chronic kidney disease.

Aims and Objectives: 1. To study efficacy of ferric citrate and sevelamer carbonate in patients of non-dialysis dependent chronic kidney disease.

2. To compare efficacy of ferric citrate and sevelamer carbonate in patients of non-dialysis dependent chronic kidney disease.

Materials and Methods: A prospective observational study to be conducted in Dayanand Medical College and Hospital, Ludhiana, Punjab, India. Including patient with non-dialysis dependent chronic kidney disease stage - III to V according KDIGO classification with hyperphosphatemia (>4.5) over a period of 12 Months including 3 months short term follow up.

Clinical significance: Despite the globalization and improvement in the diagnostic and treatment modalities in chronic kidney disease it still have high morbidity and mortality in developing countries as compared to western countries. Study, mainly focuses on to compare efficacy and safety of ferric citrate and sevelamer carbonate in a patient of Non - Dialysis dependent chronic kidney disease.

Keywords: Chronic Kidney Disease, Non-Dialysis, Ferric Citrate, Sevelamer Carbonate.

(Signature) Candidate	(Signature) Co-supervisor	(Signature) Supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON - DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE"** exist in the Department of General Medicine at Dayanand Medical College and Hospital, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself under our supervision and guidance.

Supervisor

Dr. Amit Bery
Associate Professor
Department of General Medicine
DMCH, Ludhiana

Co-Supervisor

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DMCH, Ludhiana

Head of the Department

Dr. Dinesh Gupta
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Place : _____

Date : _____

APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Nirmal Singh
Department	General Medicine
Topic of Thesis	COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON - DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE
Likely date of appearing in PG examination	May/June, 2024
Date of enrollment	March 7, 2022
Name of Head of Department	Dr Dinesh Gupta
1) Supervisor **2) Co-Supervisor**	Dr Amit Bery Dr. Preet Mohinder Singh
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Harpreet Kaur (Professor & Head, Pathology)	Mr. R K Sharma (Legal Expert)
Dr. Jaspal Singh (Professor & Head, Surgery)	Dr. Ramit Mahajan (Associate Professor, Gastroenterology)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
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Approved: Yes / ~~No~~

Dr. Sandeep Puri
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Research Committee

Chairperson
Research Committee

Approved: Yes / ~~No~~

Prof. Arvind Malhotra
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BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT
PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Nirmal Singh Village - Antor, P.O - Narot Jaimal Singh, distt - Pathankot, Punjab, India.
2	NAME OF THE INSTITUTE	Dayanand medical college and hospital, Ludhiana
3	COURSE OF STUDY AND SUBJECT	MD Medicine
4	DATE OF ADMISSION OF COURSE	04-05-2022
5	TITLE OF THE TOPIC	COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE.

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Chronic kidney disease is a major cause of morbidity and premature mortality and represents a significant global public health issue. Underlying these many complications of chronic kidney disease, are mineral and bone disorders, anemia and accelerated vascular disease. Hyperphosphatemia and elevated levels of fibroblast growth factor 23 (fgf23) has been identified as key independent risk factors for adverse cardiovascular outcomes that frequently occurs in patients with chronic kidney disease. In early chronic kidney disease serum phosphate levels are maintained within normal range by compensatory increase in parathyroid hormone (pth) anf fibroblast growth factor - 23 (fgf23) which inhibit reabsorption of phosphate by the proximal renal tubules however as chronic kidney disease progresses the risk of hyperphosphatemia increases because the limit of ability of the kidney to excrete phosphate is reached. In patient with chronic kidney disease elevated serum phosphate is associated with vascular calcification, progression of chronic kidney disease and increased mortality. Several intestinal phosphate binders are presently used to treat hyperphosphatemia in chronic kidney disease (including ferric citrate and sevelamer carbonate).

Iron deficiency in chronic kidney disease patient contribute to anemia, heart failure, central nervous system dysfunction (Cognitive) and diminished health related quality of life in patients. Whereas hyperphosphatemia can contribute to dystrophic calcification, secondary hyperparathyroidism and other abnormalities of mineral metabolism.

The optimal management strategies for iron deficiency and phosphate retention in advanced, non-dialysis dependent chronic kidney disease (ndd-ckd) are unknown.

Ferric citrate initially was developed as phosphate binder and received regulatory approval for the control of serum phosphorus in dialysis dependant chronic kidney disease (dd-ckd). When prescribed for the treatment of of hyperphosphatemia in patient of dialysis dependant chronic kidney disease (dd-ckd) it was observed that ferric citrate not only decrease serum phosphate concentrations but also increase transferrin saturation (tsat) and serum ferritin concentrations, thereby Allowing patient to maintain good hemoglobin concentration on lower dose of erythropoiesis stimulating agents (esa's) and intravenous irons.

Sevelamer carbonate has been developed as a improved buffered form of sevelamer hydrochloride. Sevelamer carbonate is anion exchange resin with the same activity moiety as sevelamer hydrochloride in which carbonate replaces chloride as an anion. The replacement of chloride with carbonate replace chloride as anion. The replacement of chloride with carbonate provides bicarbonates that may benefit a patient having chronic kidney disease and are not on dialysis and who are prone to acidosis and do not receive the benefits of renal replacement therapy. Sevelamer carbonate has the same safety and efficacy profile as sevelamer hydrochloride in hemodialysis ckd patients.

In multiple studies phosphate binders are studied for their efficacious role in controlling hyperphosphatemia and other mineral abnormalities in patient of chronic kidney disease and we have different drugs available which includes sevelamer carbonate and ferric citrate.

But the comparative efficacy in a patient of non-dialysis dependant chronic kidney disease is unknown. when compared which one is more efficacious and should be used more often for benefits of patient in reducing morbidity and premature mortality associated with chronic kidney disease. That is what this study aims to achieve.

6.2 REVIEW OF LITERATURE

Geoffrey A Block et al. (2015) did trial study of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with ckd stages 3-5 [1]. Chronic kidney disease (CKD) affects up to 13% of adults and markedly increases the risk of premature cardiovascular events. [2]. Anemia is among the most common complications of CKD and is associated with mortality and cardiovascular events, even after accounting for CKD stage and other cardiovascular risk factors, including albuminuria, diabetes mellitus, smoking, and hypercholesterolemia. [3]. Although the anemia of CKD is multifactorial in origin, 60% to 73% of persons with an estimated glomerular filtration rate (eGFR), 60 mL/min/1.73 m2 are iron deficient.[4]. Clinical practice guidelines recommend that persons with CKD and anemia (hemoglobin , 13.0 g/dL for men; 12.0 g/dL for women) be treated with iron rather than erythropoiesis-stimulating agents (ESAs) in order to increase hemoglobin level if transferrin saturation (TSAT) is #30% and serum ferritin level is #500 ng/mL. Unfortunately, conventional oral iron formulations (sulfate, fumarate, and gluconate) tend to be ineffective, [5,6]. and the provision of intravenous iron and ESAs to normalize hemoglobin levels in persons with CKD stages 3 to 5 is associated with relatively high rates of adverse effects.[7] Anaemia promotes progression of left ventricular hypertrophy and increases risk of heart failure.[8]

Glenn M Chertow. et al. (2017) studied . Safety and efficacy of ferric citrate in patients with non dialysis dependent chronic kidney disease.[9] ferric citrate when prescribed for the treatment of hyperphosphatemia in DD-CKD, investigators observed that ferric citrate not only decreased serum phosphate concentrations but also increased transferrin saturation (TSAT) and serum ferritin concentrations, allowing patients to maintain hemoglobin concentrations on lower doses of erythropoiesis-stimulating agents (ESAs) and intravenous iron [10]. ferric citrate has not been compared directly with other phosphate binders in this patient population, the achieved decrease in serum

phosphate was larger than in another randomized, placebo-controlled trial in patients with CKD stages 3–5 in which calcium acetate, sevelamer carbonate, and lanthanum carbonate were compared [11]. Trials with head-to-head comparisons would enable more definitive conclusions to be made on the relative efficacy of ferric citrate. The optimal management strategies for iron deficiency and phosphate retention in advanced, non dialysis-dependent CKD (NDD-CKD) are unknown. Ferric citrate was initially developed as a phosphate binder and received regulatory approval for the control of serum phosphorus in patients with dialysis-dependent CKD (DD-CKD) [12]. A sizeable fraction of patients treated with ferric citrate experienced a transient increase in TSAT levels above 70%, although these elevated levels were not sustained. We believe that the transient increases in TSAT reflect the fact that the blood draws were not timed relative to drug intake. As described by Kobune et al., TSAT levels can rise above 60% within 2–3 hours after intake of an oral iron dose [13].

Vincenzo Savica et al. (2008) studied Sevelamer carbonate in the treatment of hyperphosphatemia in patients with chronic kidney disease on hemodialysis.[14] Sevelamer hydrochloride is a non-calcium and non-metal quaternary amine anion exchange resin, which upon binding to a PO4 molecule by ionic and/or hydrogen bonding releases one hydrochloride molecule. For this reason, sevelamer hydrochloride has been demonstrated to worsen the metabolic acidosis that affects HD patients, leading to a serum bicarbonate threshold of 17–19 mEq/L, below the recommended K/DOQI level of 22 mEq/L.[15] Sevelamer carbonate is an anion exchange pharmaceutical, recently developed as an improvement of the non-absorbable sevelamer hydrochloride. It was developed to avoid worsening of metabolic acidosis, reported as one of the possible concerning side effects of sevelamer hydrochloride long-term treatment, and to increase patients' compliance through the development of new pharmaceutical presentation.[16] sevelamer carbonate administered at a mean actual daily dosage of 5.5 g (6–7 sevelamer carbonate 800 mg tablets per day) to CKD patients with

mean serum P ≥ 6.2 ± 0.8 mg/dL and not under replacement therapy. A significant 1.4 mg/dL decrease in serum P was observed over an 8-week treatment, after a 2-week washout for patients previously on other phosphate binders, mainly calcium-based phosphate binders. Full recovery of serum P at baseline level was reached after the 2-week post-treatment washout period. By the end of sevelamer carbonate treatment, 75% of stage 4 CKD patients (GFR 15–29 mL/min per 1.73 m2; 35% of study population) fell into the K/DOQI recommended ≥2.7 and ≤4.6 mg/dL serum P range, and 70% of stage 5 CKD patients (GFR < 15 mL/min per 1.73 m2; 65% of study population) had achieved a serum P level ≤5.5 mg/dL.[17]

Markus Ketteler, et al (2008) studied Efficacy and tolerability of sevelamer carbonate in hyperphosphatemic patients who have chronic kidney disease and are not on dialysis.[17] Sevelamer carbonate treatment resulted in statistically significant reductions in serum phosphorus. The mean serum phosphorus at the end of treatment was 4.8 mg/dl, a level well within the range of 3.5 to 5.5 mg/dl recommended for patients with stage 5 CKD (65% of the study population). Moreover, at least 70% of patients were able to achieve a serum phosphorous within the ranges recommended for CKD patients (2.7 and 4.6 mg/dl for patients with stage 4 CKD; 5.5 mg/dl for patients with stage 5 CKD). [17] This response rate is slightly higher than the 50% response rate that would be expected on the basis of similar studies in the hemodialysis population and from large scale cross-sectional studies.[18] It is unclear whether dialysis modalities in themselves change the pathophysiologic consequences of hyperphosphatemia, but it is certainly more likely that the adverse effects of hyperphosphatemia are independent of the dialysis status of a patient with CKD. The data showing the clinical consequences of hyperphosphatemia in patients who have CKD and are not on dialysis are less abundant because this population has not been closely studied, but both Kestenbaum et al. [19]. and Voormolen et al. [20] found an association between serum phosphate level and mortality in

patients who had CKD and were not on dialysis. This suggests that it is correct to consider that these patients are subject to the harmful effects of hyperphosphatemia similar to those seen in patients who are on dialysis**.**

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To study efficacy of ferric citrate and sevelamer carbonate in patients of non-dialysis dependent chronic kidney disease.
2. To compare efficacy of ferric citrate and sevelamer carbonate in patients of non-dialysis dependent chronic kidney disease.

7. MATERIALS AND METHODS

A Prospective Observational study to be conducted in Dayanand Medical College and Hospital, Ludhiana, Punjab, India. Including patient with non-dialysis dependent chronic kidney disease stage - III to V according KDIGO classification over a period of 12 Months including 3 months short term follow up.

7.1 Source of Data:

This prospective observational study which will be conducted at Dayanand medical college and hospital, Ludhiana, Punjab, India which include all patients having chronic kidney disease stage - III to V non dialysis in accordance with KDIGO (kidney disease improving global outcome) classification. It will also include written proforma containing epidemiological information of the patient age, sex, occupation, place, and patient presenting with and fulfilling the inclusion criteria of chronic kidney disease including presenting serum phosphorus levels, serum parathyroid levels, serum alkaline phosphate levels, serum TIBC, serum transferrin saturation, serum ferritin, serum bone specific alkaline phosphate levels

(if required), serum calcium levels and hemoglobin levels.

Treatment - all those patients fulfilling the inclusion criteria will be treated with either ferric citrate or sevelamer carbonate and will be monitored by repeat of samples to look for improvement or deterioration in the levels.

7.2 METHOD OF COLLECTION OF DATA

Inclusion Criterion - All patient having chronic kidney disease between stage - III to V non dialysis in accordance with KDIGO (kidney disease improving global outcome) classification with Hyperphosphatemia (>4.5) will be included in the study.

Exclusion Criterion - Patient with chronic kidney disease stage I,II and V dialysis dependent in accordance with KDIGO (kidney disease improving global outcome) classification will be excluded from the study.

DURATION OF STUDY - This is a prospective study (15 September 2022 to 15 September 2023 which includes 3 months follow up).

OUTCOME To know more efficacious and safe drug to choose for patient with chronic kidney disease stage - III to V non dialysis and to improve morbidity and mortality in patient of chronic kidney disease.

STATISTICAL ANALYSIS - Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data is normally distributed, a Kolmogorov-Smirnov test will be used. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and fisher exact test was used when the expected frequency is less than 5. A probability value (p value) less than 0.05 will be considered statistically significant. All statistical calculations will be done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows**.**

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

1. SERUM PHOSPHORUS LEVELS
2. SERUM PARATHYROID (PTH) LEVELS
3. SERUM ALKALINE PHOSPHATE (ALP) LEVELS
4. SERUM TOTAL IRON BINDING CAPACITY (TIBC)
5. SERUM TRANSFERRIN SATURATION LEVELS
6. SERUM FERRITIN LEVELS
7. SERUM BONE SPECIFIC ALKALINE LEVELS (IF REQUIRED)
8. SERUM CALCIUM LEVELS
9. SERUM HEMOGLOBIN LEVELS
10. SERUM IRON LEVELS

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith

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PROFORMA

SR.NO: MRD NO:

NAME: AGE & SEX:

ADRESS:

MONTH: (0, 3, 6, 12)

PHONE NUMBER:

CHIEF COMPLAINS:

COMORBIDITIES (IF ANY):

DIAGNOSIS

CATEGORY:

GFR:

ALBUMIN:

VITALS

BP:

HR:

SPO2:

RR:

Signature of Candidate **Signature of Supervisor**

LAB FINDING (MONTH – 0, 3, 6,12)

1.Serum Iron Levels:

2.Serum Calcium Levels:

3.Serum Ferritin Levels:

4.Serum Phosphorus Levels:

5.Serum Haemoglobin Levels:

6.Serum Parathyroid (PTH) Levels:

7.Serum Alkaline Phosphate (ALP) Levels:

8.Serum Total Iron Binding Capacity (TIBC):

9.Serum Transferrin Saturation Levels:

10.Serum Bone Specific Alkaline Levels (if required):

DRUG MANAGEMENT:

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Signature of Candidate **Signature of Supervisor**

COMMENT:_____
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Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I…….D/o, W/o, S/o……..…… am willing to participate in the study **"COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON - DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE"**

The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

……. ……

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON - DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____	_____
गवाह के हस्ताक्षर	रोगी के हस्ताक्षर/अंगूठे का निशान
नाम:	नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

“COMPARATIVE EFFICACY OF FERRIC CITRATE AND SEVELAMER CARBONATE IN PATIENTS OF NON - DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE” ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ